Improving the gastrointestinal tolerability of aspirin in older people

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Abstract: Interventions to reduce mortality and disability in older people are vital. Aspirin is cheap and effective and known to prevent cardiovascular and cerebrovascular disease, many cancers, and Alzheimer dementia. The widespread use of aspirin in older people is limited by its gastrointestinal side effects. Understanding age-related changes in gastrointestinal physiology that could put older people at risk of the side effects of aspirin may direct strategies to improve tolerance and hence lead to greater numbers of older people being able to take this effective intervention.

Keywords: aspirin, gastrointestinal side effects, gastrointestinal physiology, older people

Introduction

As the population ages, clinical and cost effective strategies to increase lifespan whilst reducing disability are becoming a major public health agenda. The cyclooxygenase inhibitor aspirin has the potential to be such a strategy, as it is a simple, cheap intervention that is increasingly recognized as preventing a wide range of diseases associated with significant morbidity, and as a result will ensure healthy life into older age.

Evidence for the benefits of aspirin is now so overwhelming that strategies to deliver it to as many older people as possible are a health promotion priority. Many cancers, strokes, myocardial infarctions, and cases of Alzheimer dementia might be prevented if more older people could benefit from the risk reductions of aspirin.

Evidence supporting the benefits of aspirin

Aspirin is one of the most frequently prescribed medications for older people (Somerville et al 1986). It is taken to control inflammation in arthritis, but more importantly has been shown in meta-analyses to reduce events in those at risk from cardiovascular or cerebrovascular disease (Antiplatelet Trialists Collaborative 2002; Hayden et al 2002). There is also emerging evidence that aspirin use protects against Alzheimer dementia and a wide range of cancers including breast, esophageal, prostate, colorectal, and lung carcinomas (Dubois et al 1998; Smith et al 2000; Bardou et al 2004).

Mathematical modeling confirms that the beneficial effects of aspirin are potentially so great that encouraging low-dose aspirin use in all 50-year-old subjects would reduce disability and double the chances of living a healthy life into old age (Morgan 2003). Many studies are now suggesting that the benefits of long-term low-dose aspirin outweigh the risks (Eidelman et al 2003). In the elderly, these benefits are to an extent similar to, and often greater than, that observed in younger age groups (Dornbrook et al 2003). However, the studies necessary to acquire such data

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Table 1 Risk factors for aspirin-induced gastrointestinal complications

- Advancing age
- Female sex
- History of peptic ulcer disease
- Type and dose of NSAID
- Duration of use
- Use of combinations of NSAIDs
- Concomitant use of drugs such as steroids or anticoagulants

Adapted from Aalykke et al (2001); Gallerani et al (2004).

in older age groups will require huge numbers such as that seen in the ongoing Aspirin in Reducing Events in the Elderly (ASPREE) study with 15 000 subjects aged over 70 being followed for 5 years (Nelson et al 2003).

Despite the acknowledged benefits of aspirin, a cross-sectional population survey found only 7.1% were taking aspirin as a primary preventative measure (Trinder et al 2003). Furthermore, of those prescribed aspirin for secondary prevention, 8% were no longer taking it at 6-month follow up, presumably because of side effects (Eagle et al 2004).

Gastrointestinal adverse effects of aspirin

The widespread use of aspirin by older people has historically been limited as many develop abdominal side effects. Almost 50% of those prescribed aspirin for secondary prevention report gastrointestinal symptoms after just 2 weeks of use (Laheij et al 2001; Niv et al 2005) and almost one-third of aspirin users have endoscopically visible lesions within one hour of ingestion (Hawkey et al 1991; Cole et al 1999). Symptoms are recognized as a poor predictor for gastrointestinal lesions with 48% of asymptomatic aspirin users having lesions visible at endoscopy.

Aspirin can lead to adverse gastrointestinal effects ranging from dyspepsia with endoscopically normal gastric mucosa, asymptomatic and symptomatic lesions such as erosions and ulcers, and complications of ulcers including bleeding and perforation. Although these gastrointestinal effects are dose dependant, even lower doses of aspirin are being increasingly recognized as a cause of gastrointestinal bleeding (Stack et al 2002).

It is controversial, however, whether simply being old makes you more susceptible to aspirin-induced gastrointestinal damage or whether comorbidity, comedications, and past history are more important predictors of toxicity than age and perhaps more relevant to therapeutic decision making in this population (Solomon and Gurwtiz 1997). Risk factors for aspirin-induced gastrointestinal complications are shown in Table 1.

Developing strategies to improve tolerability of aspirin

Gastrointestinal side effects of aspirin occur more frequently in older people (Aalykke 2001). Therefore strategies to improve tolerability might be directed in two ways: at those specific physiological abnormalities that identify individuals who are less able to tolerate aspirin irrespective of their age, and at age-related changes in gastrointestinal physiology that might predict why older people tolerate aspirin less well compared with younger age groups (Table 2). This review will focus primarily on this second strategy.

Strategies to improve tolerability: the eradication of *Helicobacter pylori*

Many changes in gastrointestinal physiology once thought to be primary effects of aging have been reexamined since the discovery of the microorganism *Helicobacter pylori* (Kateralis et al 1993; Feldman et al 1996). Infection with *H. pylori* itself induces changes in gastrointestinal physiology, which is of relevance when it is appreciated that in the Western world infection rates increase with age, with up to 80% of 80-year-old subjects infected (Marshall 1994).

Both aspirin use and *H. pylori* infection cause peptic ulcers, but whether the incidence is greater when both are present is unclear (Voutilainen et al 2001). *H. pylori* and aspirin are independent risk factors for ulceration in all age groups (Lanas et al 2002), however, studies specifically involving older people suggest that there may be a synergistic effect on risk (Ng et al 2000; Seinela and Ahvenainen 2000).

Table 2 Potential strategies to improve tolerability of aspirin in older people

***Helicobacter pylori* eradication**
Coprescription:
– With PPI
– With prostaglandin analog
Improve mucosal protective mechanisms
– Reverse the age-associated decline in mucus thickness
– Improve secretion of mucosal protective molecules, eg, TFF2
Reduce contact time by reversing the age-associated decline in gastric emptying

Abbreviations: PPI, proton pump inhibitor; TTF2, trefoil factor family 2.

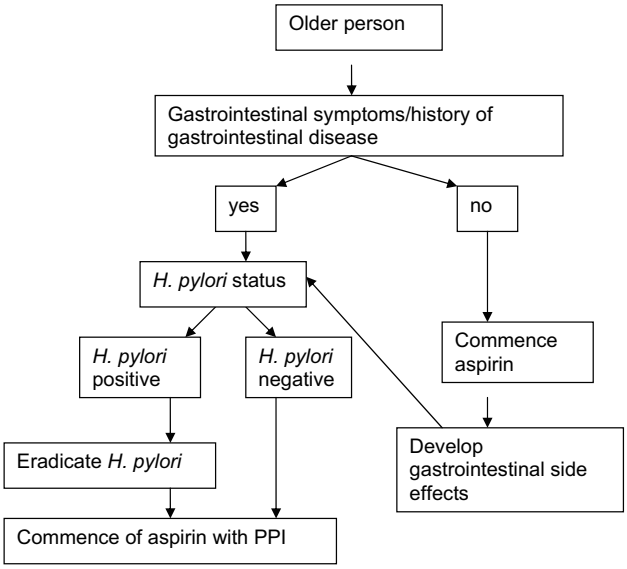

Figure 1 Proposed algorithm to improve gastrointestinal tolerance of aspirin in older people. **Abbreviations:** PPI, proton pump inhibitor.

Low doses of aspirin induced endoscopically visible upper gastrointestinal mucosal damage more frequently in *H. pylori* positive subjects (50%) compared with 16% of *H. pylori* negative volunteers (Feldman et al 2001). Furthermore, eradication of *H. pylori* reduces damage caused by low doses of aspirin and recurrence of ulcers during aspirin use (McCarthy 1998) and improves adaptability of the gastrointestinal tract to aspirin (Konteruk et al 1997, 1998). Unfortunately, *H. pylori* eradication will not always improve aspirin tolerability, as gastrointestinal symptoms, ulcers, and their complications are associated with aspirin use in those with, and without, *H. pylori* infection (Seinela and Ahvenainen 2000).

Despite this, it would seem pragmatic to recommend eradication of *H. pylori* infection prior to commencing long-term aspirin treatment. Whether or not this approach is appropriate in all older people, irrespective of symptoms, or only in those with gastrointestinal symptoms or a history of peptic ulceration (NICE 2005) requires large studies in older people and should include evaluation of aspirin tolerance after *H. pylori* eradication (Figure 1).

Structural changes with age in the upper gastrointestinal tract could affect tolerance of aspirin

Gastrointestinal transit time, in particular gastric emptying, is slower in older people (Brogna et al 1999), which potentially increases exposure of the gastric mucosa to ingested drugs. Such direct toxic effects provide the rationale for the use of enteric-coated aspirin. Theoretically, influencing the time of exposure to, or the formulation of, aspirin preparations, or reversing the age-associated decline in gastrointestinal transit time, may influence the ability of older people to tolerate aspirin.

Atrophy of the gastric mucosa incidence increases with age (James 2000) partly because of the increased prevalence of *H. pylori* in older people. Gastric atrophy results in smaller volumes of less acidic gastric juice in the stomach lumen. This reduced ability to dilute ingested drugs will potentially increase the risk of direct gastrointestinal toxic side effects. Further study is required to determine whether widespread *H. pylori* eradication programmes would decrease gastric atrophy prevalence in older people and allow better tolerance of aspirin.

Improving tolerance of aspirin by addressing age-related changes in gastrointestinal physiology

There is limited research examining age-related changes in the human upper gastrointestinal tract that might explain why older people tolerate aspirin less well. What is currently known about changes in physiology in the older stomach and duodenum is summarized in Figure 2. An understanding of these changes in gastric physiology with age could direct interventions that lead to improved tolerance.

In the human gastrointestinal tract there is a balance between aggressive factors (gastric acid and pepsin) and mucosal protective mechanisms (mucus and bicarbonate). Current evidence does not suggest that the increase in dyspeptic symptoms or ulceration in older people taking

Luminal effects
↓ transit time
↓ gastric emptying
↑ gastric atrophy
- ↓ volume of gastric juice
  - ↓ dilution of noxious agents
- ↓ acid production
  - ↓ ability to activate acid dependant medications
  - ↓ altered bioavailability of modified release preparations

Mucosal protection
↓ bicarbonate
↓ mucus protection
↓ prostaglandin

Repair processes
↓ reparative capacity of the epithelium
↓ blood supply

Figure 2 Age-related changes in gastrointestinal physiology.

aspirin is related to an age-related increase in the aggressive factors: gastric acid or pepsin. Gastric acid secretion may be reduced in older people due to the increase in gastric atrophy, and pepsin output is also lower (Feldman et al 1996). However, age-related deficiencies in the ability of the mucosa to protect and repair itself have been documented, and any additional depletion due to medication such as aspirin will further increase mucosal vulnerability (Guslandi et al 1999).

Gastrointestinal mucosal protective molecules such as prostaglandins decline with advancing age (Cryer, Lee, et al 1992; Cryer, Redfern, et al 1992; Goto et al 1992; Lee and Feldman 1994). Prostaglandins stimulate protective mechanisms such as mucus and bicarbonate whilst aspirin inhibits prostaglandin production and causes gastric damage (Sababi et al 1995). The lower levels of prostaglandins in the gastric mucosa of older people makes them more susceptible to damage by a further reduction in prostaglandin synthesis caused by aspirin.

The first line of mucosal protection from exogenous toxins and luminal acid and pepsin is the mucus gel layer. Studies have shown both a quantitative reduction in mucus production with age and impaired quality of the mucus (Corfield et al 1993; Farinati et al 1993; Newton, Jordan et al 2000), and as a result an increased susceptibility to damage by aspirin (Corfield et al 1993).

The ability of the gastric mucosa to protect itself by repelling toxins is independently decreased in association with *H. pylori* induced gastritis and NSAID use (Goddard et al 1987; Spychal et al 1990) and also with aging (Hackelsberger et al 1998). It is not clear whether these factors work synergistically.

There is also an age-related decline in the ability of the gastrointestinal mucosa to neutralize luminal acid by bicarbonate secretion (Kim et al 1990; Lee 1997; Feldman et al 1998; Guslandi et al 1999). The older stomach is also less able to repair itself after damage (Lee et al 1998; Liu et al 1998), which when taken with the antithrombotic effects of aspirin may account for gastrointestinal side effects. Control of the repair processes is poorly understood but does have the potential to be manipulated (Majumdar et al 1997). Trefoil proteins are a family of mucosal repair proteins thought to be important in gastrointestinal protection (May and Westley 1997). Trefoil factor family 1 (TFF1) and TFF2 are expressed in the stomach and TFF2 and TFF3 are expressed in the duodenum. TFF1 is intimately associated with gastric mucus (Newton, Allen, et al 2000) and gastric concentrations of TFF2 show a circadian variation (Semple et al 2001) increasing dramatically at night. Recent work by our group has shown that the nocturnal peak of mucosally protective TFF2 is lower and earlier in older people (Johns et al 2005), and manipulating the nocturnal increase of cytoprotective TFF2 or encouraging patients to take aspirin at night when the mucosal protective mechanisms are optimal may improve tolerability.

In animals, a reduction in basal gastric blood flow (Lee 1996) and an attenuation of gastric blood flow in response to injury has been observed with age (Gronbech and Lacy 1994; Miyake et al 1996), though this is controversial (Taha 1993). If there are reductions in gastric blood flow in older people, coprescription of the vasodilator nitric oxide with aspirin (NO-NSAID) may have potential (Wallace et al 1995).

Strategies known to reduce gastrointestinal complications of aspirin in older people

Studies carried out specifically in older age groups have shown in both acute and chronic users of aspirin, that concomitant use of a proton pump inhibitor (PPI) reduces the risk of gastrointestinal bleeding (odds ratio [OR] 1.12 chronic, 1.05, acute) (Pilotto et al 2003) and risk of peptic ulcer disease (Pilotto et al 2004).

This benefit from PPI coprescription with aspirin is greater than with either the prostaglandin analog misoprostol (OR 1.91) and H2 blockers (OR 2.26). This has prompted the recommendation that PPI cotreatment is advisable in symptomatic older patients who need treatment with aspirin. However, whether a similar approach is appropriate for primary prevention of complications in asymptomatic older people requiring aspirin needs study.

In addition, although the studies confirm that both PPI and misoprostol are effective at reducing the risk of ulcer recurrence (Goldstein et al 2004), this does not guide clinical practice when confronted with a patient who simply develops gastrointestinal symptoms (rather than complications) after commencing aspirin.

Some have suggested that in high-risk patients with aspirin-associated peptic ulcer disease, conversion to other antiplatelet therapies such as clopidogrel may be appropriate. However, studies suggest that complication rates with clopidogrel are no better than continuation of aspirin alone (Ng et al 2004), with studies confirming that aspirin plus PPI is superior to clopidogrel in the prevention of recurrence (Chan et al 2005).

Patients taking long-term, low-dose aspirin who have had ulcer complications respond to acid suppressive treatments such as a PPI after eradication of *H. pylori* (Lai et al 2002), but eradication alone may be superior to the use of a PPI (Chan et al 2001). It should be remembered that coprescription of acid suppressive treatments with aspirin to improve tolerability in older people is unlikely to be the whole answer as physiologically there is no age-related increase in acid.

Future directions

Damage to the gastrointestinal mucosa is related to aspirin dose (Moore et al 1989, 1991) and lower doses of aspirin have fewer side effects (Serrano et al 2002). Therefore, it may be that some aspirin is better than no aspirin, and studies in older age groups would determine whether smaller doses of aspirin could be tolerated and give some, if not all, of the benefits obtained with larger doses in younger age groups. In the past, treatment of those who developed adverse side effects was terminated. The evidence for the use of aspirin is now so overwhelming that we need to consider how to give some aspirin to as many people as possible.

There are huge implications for allowing greater numbers of older people to benefit from taking aspirin for prevention of cardiovascular and cerebrovascular disease, Alzheimer dementia, and cancer. Defining the underlying age-related changes in physiology that make the older gastrointestinal tract susceptible to damage will identify targets for therapy. Reducing deficiencies in mucosal repair proteins, such as growth factors and trefoil proteins, may improve the reparative process. Delineating the pathways of action of these molecules in older people is therefore important. Conceptually simple strategies such as reducing the prevalence of gastric atrophy or reversing the age-associated decline in gastric emptying may also be effective.

Conclusion

Aging of the stomach and duodenum is an important but poorly understood area of gerontology. In older people, the major causes of mortality and morbidity are cardiovascular and cerebrovascular diseases, gastrointestinal cancers, and dementia. Understanding how aspirin reduces risk in these diseases and whether or not older people are intrinsically at risk of side effects because of age-related changes in gastrointestinal physiology should allow greater numbers of older people to benefit from the risk reductions associated with taking aspirin. Research in this area could be translated directly into the clinical setting and potentially make a real impact upon the quality of life of older people.

References

Aalykke C, Lauritsen K. 2001. Epidemiology of NSAID-related gastroduodenal mucosal injury. *Best Pract Res Clin Gastroenterol*, 15:704–22.

Antiplatelet Trialists Collaboration. 2002. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ*, 324: 71–86.

Bardou M, Barkun AN, Ghosn J, et al. 2004. Effect of chronic intake of NSAID and cyclooxygenase 2 selective inhibitors on oesophageal cancer incidence. *Clin Gastroenterol Hepatol*, 2:880–7.

Brogna A, Ferrara R, Bucceri AM, et al. 1999. Influence of ageing on gastrointestinal transit time: an ultrasonographic and radiologic study. *Invest Radiol*, 34:357–9.

Chan FK, Ching JYL, Hung LCT, et al. 2005. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *NEJM*, 352: 238–44.

Chan FK, Chung SC, Suen BY, et al. 2001. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low dose aspirin or naproxen. *NEJM*, 344:967–73.

Cole AT, Hudson N, Liew LC, et al. 1999. Protection of human gastric mucosa against aspirin – enteric coating or dose reduction? *Aliment Pharmacol Ther*, 13:187–93.

Corfield AP, Wagner SA, Safe A, et al. 1993. Sialic acids in human gastric aspirates: detection of 9-O-lactyl- and 9-O-acetylneuraminic acids and a decrease in total sialic acid concentration with age. *Clin Sci*, 84: 573–9.

Cryer B, Lee E, Feldman M. 1992. Factors influencing gastroduodenal mucosal prostaglandin concentrations: roles of smoking and aging. *Ann Intern Med*, 116:636–40.

Cryer B, Redfern S, Goldschiedt M, et al. 1992. Effect of aging on gastric and duodenal mucosal prostaglandin concentrations in humans. *Gastroenterology*, 102:1118–23.

Dornbrook LKA, Pieper JA, Roth MT. 2003. Primary prevention of coronary heart disease in the elderly. *Ann Pharmacother*, 37: 1654–63.

Dubois RN, Abramson SB, Crofford L, et al. 1998. Cyclooxygenase in biology and disease. *FASEB J*, 12:1063–73.

Eagle KA, Kline RE, Goodman S, et al. 2004. Adherence to evidence based therapies after discharge for acute coronary syndromes: an ongoing prospective observational study. *AJM*, 117:73–81.

Eidelman RS, Hebert PR, Weisman SM, et al. 2003. An update on aspirin in the primary prevention of cardiovascular disease. *Arch Inter Med*, 163:2006–10.

Farinati F, Formentini S, Della Libera G, et al. 1993. Changes in parietal cell and mucous cell mass in the gastric mucosa of normal subjects with age: a morphometric study. *Gerontology*, 39:146–51.

Feldman M, Cryer B. 1998. Effects of normal aging on gastric non-parietal fluid and electrolyte secretion in humans. *Gerontology*, 44:222–7.

Feldman M, Cryer B, Mallat D, et al. 2001. Role of Helicobacter pylori infection in gastrointestinal injury and gastric prostaglandin synthesis during long term/low dose aspirin therapy: a prospective placebo-controlled, double blind randomized trial. *Am J Gastroenterol*, 96:1751–7.

Feldman M, Cryer B, McArthur KE, et al. 1996. Effects of aging and gastritis on gastric acid and pepsin secretion in humans: a prospective study. *Gastroenterology*, 110:1043–52.

Gallerani M, Simonata M, Manfredini R, et al. 2004. Risk of hospitalisation for upper gastrointestinal tract bleeding. *J Clin Epidemiol*, 57: 103–10.

Goddard PJ, Hills BA, Lichtenberger LM. 1987. Dose aspirin damage canine gastric mucosa by reducing surface hydrophobicity. *Am J Physiol*, 252:G421–30.

Goldstein JL, Huang B, Christopoulos NG, et al. 2004. Ulcer recurrence in high risk patients receiving nonsteroidal anti-inflammatory drugs plus low dose aspirin: results in post hoc subanalysis. *Clin Ther*, 26:1637–43.

Goto H, Sugiyama S, Ohara A, et al. 1992. Age associated decreases in prostaglandin contents in human gastric mucosa. *Biochem Biophys Res Commun*, 186:1443–8.

Gronbech JE, Lacy ER. 1994. Impaired gastric defense mechanisms in aged rats: role of sensory neurons, blood flow, restitution and prostaglandins. *Gastroenterology*, 106:A84.

Guslandi M, Pellegrini A, Sorghi M. 1999. Gastric mucosal defences in the elderly. *Gerontology*, 45:206–8.

Hackelsberger A, Platzer U, Nilius M, et al. 1998. Age and Helicobacter pylori decrease gastric mucosal surface hydrophobicity independently. *Gut*, 43:465–9.

Hawkey CJ, Hawthorne AB, Hudson N, et al. 1991. Separation of the impairment of homeostasis by aspirin from mucosal injury in the human stomach. *Clin Sci*, 81:565–73.

Hayden M, Pignone M, Phillips C, et al. 2002. Aspirin for the primary prevention of cardiovascular events: a summary of evidence for the US Preventive Services Task Force. *Ann Intern Med*, 136:161–72.

James OFW. 2000. The stomach. Grimley-Evans J, Franklin-Williams T (eds). The Oxford textbook of geriatric medicine. Oxford: Oxford Univ Pr. p 179–256.

Johns CE, Newton JL, Westley BR, et al. 2005. The diurnal rhythm of the cytoprotective trefoil protein TFF2 is reduced by factors associated with gastric morbidity: ageing, Helicobacter pylori infection and sleep deprivation. *Am J Gastroenterol*, 100:1491–7.

Kateralis PH, Seow F, Lin BPC, et al. 1993. Effect of age, Helicobacter pylori infection, gastritis with atrophy on serum gastrin and gastric acid secretion in healthy men. *Gut*, 34:1032–7.

Kim SW, Parekh D, Townsend CM, et al. 1990. Effects of aging on duodenal bicarbonate secretion. *Ann Surg*, 212:332–8.

Konteruk JW, Deminski A, Konturek SJ, et al. 1997. Helicobacter pylori and gastric adaptation to repeated aspirin administration in humans. *J Physiol Pharmacol*, 48:383–91.

Konteruk JW, Deminski A, Konturek SJ, et al. 1998. Infection of Helicobacter pylori in gastric adaptation to continued administration of aspirin in humans. *Gastroenterology*, 114:245–55.

Laheij RJ, Jansen JB, Verbeek AL, et al. 2001. Helicobacter pylori infection as a risk factor for gastrointestinal symptoms in patients using aspirin to prevent ischaemic heart disease. *Aliment Pharmacol Ther*, 15: 1055–9.

Lai KC, Lam SK, Chu KM, et al. 2002. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *NEJM*, 346:2033–8.

Lanas A, Fuentes J, Benito R, et al. 2002. Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther*, 16:779–86.

Lee M. 1996. Age-related changes in gastric blood flow in rats. *Gerontology*, 42:290–3.

Lee M. 1997. The aging stomach: implications for NSAID gastropathy. *Gut*, 41:425–6.

Lee M, Feldman M. 1994. Age-related reductions in gastric mucosal prostaglandin levels increase susceptibility to aspirin-induced injury in rats. *Gastroenterology*, 107:1746–50.

Lee M, Hardman WE, Cameron I. 1998. Age-related changes in gastric mucosal repair and proliferative activities in rats exposed acutely to aspirin. *Gerontology*, 44:198–203.

Liu L, Tuner JR, Yu Y, et al. 1998. Differential expression of EGFR during the early reparative phase of the gastric mucosa between young and aged rats. *Am J Physiol*, 275:G943–50.

Majumdar AP, Fligiel SE, Jaszewski R. 1997. Gastric mucosal injury and repair: effect of ageing. *Histol Histopathol*, 12:491–501.

Marshall BJ. 1994. Helicobacter pylori. *Am J Gastroenterol*, 89:S116–28.

May FEB, Westley BR. 1997. Trefoil proteins: their role in normal and malignant cells. *J Pathol*, 183:4–7.

McCarthy DM. 1998. Helicobacter pylori and non-steroidal antiinflammatory drugs: does infection affect the outcome of NSAID therapy? *Yale J Biol Med*, 71:101–11.

Milani S, Calabro A. 2001. Role of growth factors and their receptors in gastric ulcer healing. *Microsc Res Tech*, 53:360–71.

Miyake H, Inaba N, Kato S, et al. 1996. Increased susceptibility of rat gastric mucosa to ulcerogenic stimulation with aging: role of capsaicin sensitive sensory neurons. *Dig Dis Sci*, 41:339–45.

Moore JG, Bjorkman DJ. 1989. NSAID-induced gastropathy in the elderly: understanding and avoidance. *Geriatrics*, 44:51–7.

Moore JG, Bjorkman DJ, Mitchell MD, et al. 1991. Age does not influence acute aspirin-induced gastric mucosal damage. *Gastroenterology*, 100:1626–9.

Morgan G. 2003. A quantitative illustration of the public health potential of aspirin. *Med Hypotheses*, 60:900–2.

Nelson M, Reid C, Beillin L, et al. 2003. Rationale for a trial of low dose aspirin for the primary prevention of major adverse cardiovascular events and vascular dementia in the elderly. Aspirin for reducing events in the elderly (ASPREE). *Drugs Aging*, 20:897–903.

Newton JL, Allen A, Westley BR, et al. 2000. The human trefoil peptide, TFF1, is present in different molecular forms that are intimately associated with mucus in normal stomach. *Gut*, 46:312–20.

Newton JL, Jordan N, Pearson J, et al. 2000. The adherent gastric antral and duodenal mucus layer thins with advancing age in subjects infected with Helicobacter pylori. *Gerontology*, 46:153–7.

Ng FH, Wong BCY, Wong SY, et al. 2004. Clopridogrel plus omeprazole compared with aspirin plus omeprazole for aspirin-induced symptomatic peptic ulcers/ erosions with low to moderate bleeding/ re-bleeding risk – a single-blind, randomised controlled study. *Aliment Pharmacol Ther*, 19:359–65.

Ng TM, Foack KM, Khor JL, et al. 2000. Nonsteroidal antiinflammatory drugs, Helicobacter pylori and bleeding gastric ulcer. *Aliment Pharmacol Ther*, 14:203–9.

NICE. 2005. NICE dyspepsia guidelines in primary care. [online]. Accessed 19 Aug 2005. URL: http://www.nice.org.uk/pdf/CG017NICE guideline.pdf.

Niv Y, Battler A, Abuksis G, et al. 2005. Endoscopy in asymptomatic minidose aspirin consumers. *Dig Dis Sci*, 50:78–80.

Pilotto A, Franceschi M, Leandro G, et al. 2003. The risk of upper gastrointestinal bleeding in elderly users of aspirin and other non-steroidal anti-inflammatory drugs: the role of gastroprotective drugs. *Aging Clin Exp Res*, 15:494–9.

Pilotto A, Franceschi M, Leandro G, et al. 2004. Proton pump inhibitors reduce the risk of uncomplicated peptic ulcer in elderly either acute or chronic users of aspirin/non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther*, 20:1091–7.

Sababi M, Nilsson E, Holm L. 1995. Mucus and alkali secretion in the rat duodenum: effects of indomethacin, N-nitro-L-arginine and luminal acid. *Gastroenterology*, 109:1526–34.

Seinela L, Ahvenainen J. 2000. Peptic ulcer in the very old patients. *Gerontology*, 46:271–5.

Semple JI, Newton JL, Westley BR, et al. 2001. Dramatic diurnal variation in the concentration of the human trefoil peptide TFF2 in gastric juice. *Gut*, 48:648–55.

Serrano P, Lanas A, Arroyo MT, et al. 2002. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. *Aliment Pharmacol Ther*, 16:1945–53.

Smith WL, DeWitt DL, Garavito RM. 2000. Cyclooxygenases: structural, cellular, and molecular biology. *Annu Rev Biochem*, 69:145–82.

Solomon DH, Gurwtiz JH. 1997. Toxicity of nonsteroidal antiinflammatory drugs in the elderly: is advanced age a risk factor? *Am J Med*, 102: 208–15.

Sommerville K, Faulkner G, Langman MJS. 1986. Nonsteroidal antiinflammatory drugs and bleeding peptic ulcer. *Lancet*, 1:464–5.

Spychal RT, Goggin PM, Marrer JM, et al. 1990. Surface hydrophobicity of gastric mucosa in peptic ulcer disease- relationship to gastritis and campylobacter pylori infection. *Gastroenterology*, 98:1250–4.

Stack WA, Atherton JC, Hawkey GM, et al. 2002. Interactions between Helicobacter pylori and other risk factors for peptic ulcer bleeding. *Aliment Pharmacol Ther*, 16:497–506.

Taha AS, Angerson W, Nakshabendi I, et al. 1993. Gastric and duodenal mucosal blood flow in patients receiving non-steroidal anti-inflammatory drugs – influence of age, smoking, ulceration and Helicobacter pylori. *Aliment Pharmacol Ther*, 7:41–5.

Trinder P, Rajaratnam G, Lewis M, et al. 2003. Prophylactive aspirin use in the adult general population. *J Public Health Med*, 25:377–80.

Wallace JL, McKnight W, Del Soldata P, et al. 1995. Antithrombotic effects of nitric-oxide releasing gastric sparing aspirin derivative. *J Clin Invest*, 96:2711–18.

Voutilainen M, Mantynen T, Farkkila M, et al. 2001. Impact of nonsteroidal antiinflammatory drug and aspirin use on the prevalence of dyspepsia and uncomplicated peptic ulcer disease. *Scand J Gastroenterol*, 36:817–21.