

Aging and the alimentary tract

The aging stomach: implications for NSAID gastropathy

Over 30 million people worldwide use non-steroidal anti-inflammatory drugs (NSAIDs) daily, and nearly 50% of these NSAID users are elderly.^{1,2} Numerous human studies have shown that the use of NSAIDs is associated with various gastroduodenal mucosal lesions,^{2–4} sometimes collectively referred to as NSAID gastropathy,⁴ and that NSAID gastropathy and its life-threatening complications occur primarily in elderly patients.^{5,6} Overall, the use of NSAIDs increases the risk of peptic ulcer disease, ulcer complications (haemorrhage and/or perforation), and death from ulcer by a factor of between 2 and 4.^{3,5,7} In the United States alone, medical costs attributable to NSAID gastropathy and its complications exceed \$4 (£2.4) billion a year.² Although increased NSAID use among the elderly is an obvious risk factor, epidemiological data suggest that aging is an independent risk factor for the development of NSAID gastropathy and its complications.^{5,6,8} The aim of this article is to review recent developments in the area of age related changes in gastric physiology that may predispose the elderly to NSAID gastropathy. A better understanding of the age related changes in gastric mucosal functions will help us to develop novel interventions for the treatment and prevention of NSAID induced gastrointestinal injury in susceptible elderly people.

Mechanisms of NSAID induced gastric mucosal injury

The mechanisms by which aspirin and other NSAIDs produce acute and chronic gastroduodenal mucosal injury are incompletely understood. In general, gastric mucosal injury is thought to result when aggressive luminal factors (such as acid and pepsin) overwhelm local mucosal protective factors (such as mucus and bicarbonate).^{8,9} Results from animal studies suggest that the production of mucosal lesions by aspirin is a result of two independent mechanisms: (a) cyclooxygenase inhibition by aspirin; and (b) topical effects induced by salicylate, the product of aspirin deacetylation.^{8,9} The salicylate induced toxic effects include changes in transmembrane permeability, electrical activity, metabolism, and ion transport; whereas cyclooxygenase inhibition and resultant changes in eicosanoid metabolism may result in alterations or reductions in gastric mucosal defensive functions, which include, but are not limited to, bicarbonate and mucus secretion, proliferation and repair, blood flow, and growth factor expression.^{8,9}

Age related changes in aggressive luminal factors

Gastric acid and pepsin are the major aggressive luminal factors in humans and experimental animal models.^{8,9} Several groups of investigators have recently reported that gastric acid secretion in humans changes little with normal aging, unless there is co-existent gastric pathology.^{10–12} In general, the vast majority of healthy, elderly people have normal gastric secretion, while a small fraction have acid hyposecretion because of chronic atrophic gastritis.^{10–13} Moreover, advancing age is associated with modestly reduced pepsin output in humans independent of atrophic gastritis, *Helicobacter pylori* infection and smoking.¹⁴ On the other hand, there is limited information from animal models on the effects of aging on gastric secretion. In Fischer 344 rats, aging reduces the capacity of the gastric mucosa

to secrete acid¹⁵ and pepsin,¹⁶ and these age related changes in gastric secretion are associated with reductions in serum and antral gastrin concentrations.¹⁵ Taken together, available data do not support the notion that age related increases in luminal aggressive factors (such as acid and pepsin) contribute to the increased incidence of gastric ulceration in the elderly population exposed to NSAIDs. Hence, the alternative hypothesis will be that the increased susceptibility to NSAID gastropathy among the elderly is a result of alterations or reductions in gastric mucosal protective factors.

Age related changes in gastric mucosal defence

Two human studies^{17,18} have demonstrated that gastric mucosal prostaglandin content declines with age in humans, and animal studies have yielded similar results.^{19,20} Uchida *et al* have demonstrated that gastric mucosal prostaglandin biosynthesis declines with age in rats, and that the aged rats are more likely to develop gastric ulcerations following serosal application of acetic acid.¹⁹ In another study, Lee *et al* have shown that gastric mucosal prostaglandin synthesis decreases with age in rats and that aged animals are more susceptible to aspirin induced acute gastric mucosal injury.²⁰ These observations suggest that aging may impair gastric mucosal prostaglandin synthesis and other protective mechanisms against various noxious substances.

Gastric bicarbonate and mucus are secreted by non-parietal gastric epithelial cells, providing an alkaline gel layer which serves as the first layer of defence against luminal acid-pepsin and exogenous noxious substances such as NSAIDs.^{8,9} In a recent human study, Feldman and Cryer have shown that advancing age is associated with a significant decline in gastric bicarbonate, sodium ion and non-parietal fluid secretion, while no age related changes in acid and parietal fluid secretion are noted.²¹ These observations are in agreement with data from a recent animal study showing that aging was associated with significantly lower gastric luminal pH and bicarbonate output in the rat stomach and that aging also blunted the prostaglandin mediated increases in gastric bicarbonate secretion in rats.²² Moreover, Kim *et al* have shown in anaesthetised Fischer 344 rats that although aging does not affect basal duodenal bicarbonate secretion, the duodenal bicarbonate response to a fixed load of luminal acid declines progressively with age.²³ Although there is no published information on the effects of aging on gastric mucus contents in humans, a preliminary report suggests that aging is associated with selective and specific changes in gastric mucus content and production in rats.²⁴ In Fischer 344 rats, a significant reduction in the acidic mucus content of the stomach is noted in aged rats, with no significant changes in neutral mucus noted in any age groups.²⁴ Although aging does not affect basal gastric mucin glycoprotein synthesis in rats, aging blunts the increase in mucin glycoprotein synthesis in rats exposed acutely to an injurious dose of aspirin.²⁴

The issue of aging and gastric mucosal proliferation and regeneration has mostly been investigated in animal models. Hinsull has shown that aged male WAB rats have reductions in the numbers and content of gastric mucosal

epithelial cells compared with young male rats, and that this change is associated with gastric mucosal erosions in aged rats.²⁵ Furthermore, the rate of proliferation of stem cells in the neck of the gastric glands is reduced in aged rats.²⁵ Majumdar *et al* have reported that aged rats are more susceptible to hypertonic saline induced acute gastric injury, and that the magnitude of gastric mucosal proliferative response is higher in young rats than in aged rats.²⁶ Subsequent mechanistic studies have demonstrated that aging is associated with diminished regenerative capacity of gastric mucosa that has been damaged by hypertonic saline^{27, 28}; and this age related deficiency in mucosal repair is secondary to reduced expression of various growth factors (such as transforming growth factor α)²⁸ and growth factor receptor related enzymes (such as tyrosine kinases)^{27, 28} in the stomachs of aged rats.

Gastric mucosal blood flow plays an important role in maintaining the gastric mucosal integrity and contributing to mucosal repair by supplying oxygen and nutrients and by removing injurious agents and phlogogenic substances.^{8, 9} Although there is little published information on the effects of aging on gastric mucosal blood flow in humans, two recent animal studies^{29, 30} have shown that aging significantly affects gastric blood flow. Lee has reported that aging is associated with a significant decline in basal gastric blood flow, whereas there is no significant difference in acid induced increases in gastric blood flow between young and aged rats.²⁹ In another study, Miyake *et al* reported that gastric mucosa of aged rats is more vulnerable to acid back-diffusion following acute mucosal injury because of dysfunction of gastric mucosal blood flow responses mediated by capsaicin sensitive sensory neurons in the presence of mucosal disruption and acid back-diffusion.³⁰

Taken together, recent animal studies suggest that aging is associated with selective and specific changes in gastric mucosal defensive mechanisms that may predispose aged animals to gastric mucosal injury.

Conclusion

A review of human and animal studies indicates that while there is little or no change in gastric luminal aggressive factors with normal aging, advancing age is associated with significant alterations in various gastric mucosal defence mechanisms and diminished responsiveness to injury. These age related changes in gastric mucosal defence may explain the predisposition of elderly people to gastric ulcer disease, especially in the setting of NSAID use.

MAKAU LEE

Department of Medicine,
University of Texas Health Science Center,
7703 Floyd Curl Drive,
San Antonio, Texas 78284-7878, USA

MARK FELDMAN

Department of Medicine,
University of Texas Southwestern Medical Center
and Veterans Affairs Medical Center,
Dallas, Texas 75216, USA

Correspondence to: Dr Lee.

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- Baum C, Kennedy DL, Forbes MB. Utilization of nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1985; **28**: 686-92.
- Kendall BJ, Peura DA. NSAID-associated gastrointestinal damage and the elderly. *Practical Gastroenterology* 1993; **17**: 13-29.
- Somerville K, Faulkner G, Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. *Lancet* 1986; **i**: 462-4.
- Roth SH. Nonsteroidal anti-inflammatory drug gastropathy. *Arch Intern Med* 1986; **146**: 1075-6.
- Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. *Ann Intern Med* 1988; **109**: 359-63.
- Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 1991; **114**: 257-63.
- Bloom BS. Risk and cost of gastrointestinal side effects associated with nonsteroidal antiinflammatory drugs. *Arch Intern Med* 1989; **149**: 1019-22.
- Soll AH, Weinstein WM, Kurata J, McCarthy D. Nonsteroidal anti-inflammatory drugs and peptic ulcer disease. *Ann Intern Med* 1991; **114**: 307-19.
- Kauffman G. Aspirin-induced gastric mucosal injury: lessons learned from animal models. *Gastroenterology* 1989; **96**: 606-14.
- Goldschmidt M, Barnett CC, Schwarz BE, Karnes WE, Redfern JS, Feldman M. Effect of age on gastric acid secretion and serum gastrin concentrations in healthy men and women. *Gastroenterology* 1991; **101**: 977-90.
- Katellaris PH, Seow F, Lin BPC, Napoli J, Ngu MC, Jones DB. Effect of age, Helicobacter pylori infection, and gastritis with atrophy on serum gastrin and gastric acid secretion in healthy men. *Gut* 1993; **34**: 1032-7.
- Collen MJ, Abdulian JD, Chen YK. Age does not affect basal gastric acid secretion in normal subjects or in patients with acid-peptic disease. *Am J Gastroenterol* 1994; **89**: 712-6.
- Krasinski SD, Russell RM, Samloff IM, Jacob RA, Dallal GE, McGandy RB, Hartz SC. Fundic atrophic gastritis in an elderly population. *J Am Geriatr Soc* 1986; **34**: 800-6.
- Feldman M, Cryer B, McArthur KE, Huet BA, Lee E. Effects of aging and gastritis on gastric acid and pepsin secretion in humans: a prospective study. *Gastroenterology* 1996; **110**: 1043-52.
- Khalil T, Singh P, Fujimura M, Townsend CM, Thompson, JC. Effect of aging on gastric acid secretion, serum gastrin, and antral gastrin content in rats. *Dig Dis Sci* 1988; **33**: 1544-8.
- Maitra RS, Edgerton EA, Majumdar APN. Gastric secretion during aging in pylori-ligated rats and effects of pentagastrin. *Exp Gerontol* 1988; **23**: 463-72.
- Cryer B, Redfern JS, Goldschmidt M, Lee E, Feldman M. Effect of aging on gastric and duodenal mucosal prostaglandin concentrations in humans. *Gastroenterology* 1992; **102**: 1118-23.
- Goto H, Sugiyama S, Ohara A, Hoshino H, Hamajima E, Kanamori S, *et al*. Age-associated decreases in prostaglandin contents in human gastric mucosa. *Biochem Biophys Res Commun* 1992; **186**: 1443-8.
- Uchida M, Kawano O, Misaki N, Saitoh K. Healing of acetic acid-induced gastric ulcer and gastric mucosal PGI₂ level in rats. *Dig Dis Sci* 1990; **35**: 80-5.
- Lee M, Feldman M. Age-related reductions in gastric mucosal prostaglandin levels increase susceptibility to aspirin-induced injury in rats. *Gastroenterology* 1994; **107**: 1746-50.
- Feldman M, Cryer B. Effects of normal aging on gastric nonparietal fluid and electrolyte secretion in humans. *Gerontology* (in press).
- Lee M. Age-related changes in gastric mucosal bicarbonate secretion in rats. *Age* 1996; **19**: 55-8.
- Kim SW, Parekh D, Townsend CM, Thompson JC. Effects of aging on duodenal bicarbonate secretion. *Ann Surg* 1990; **212**: 332-8.
- Lee M, Feldman M. Age-related changes in gastric mucosal glycoprotein synthesis in rats basally and in response to acute aspirin exposure [abstract]. *Gastroenterology* 1993; **104**: A131.
- Hinsull SM. Effect of colloidal bismuth subcitrate on age related gastric lesions in the rat. *Gut* 1991; **32**: 355-60.
- Majumdar APN, Moshier JA, Arlow FL, Luk GD. Biochemical changes in the gastric mucosa after injury in young and aged rats. *Biochim Biophys Acta* 1989; **992**: 35-40.
- Fligel SEG, Relan NK, Dutta S, Tureaud J, Hatfield J, Majumdar APN. Aging diminishes gastric mucosal regeneration: relationship to tyrosine kinases. *Lab Invest* 1994; **70**: 764-74.
- Relan NK, Fligel SEG, Dutta S, Tureaud J, Chanhhan DP, Majumdar APN. Induction of EGF-receptor tyrosine kinase during early reparative phase of gastric mucosa and effects of aging. *Lab Invest* 1995; **73**: 717-26.
- Lee M. Age-related changes in gastric blood flow in rats. *Gerontology* 1996; **42**: 290-3.
- Miyake H, Inaba N, Kato S, Takeuchi K. Increased susceptibility of rat gastric mucosa to ulcerogenic stimulation with aging: role of capsaicin-sensitive sensory neurons. *Dig Dis Sci* 1996; **41**: 339-45.