SELECTION SUMMARIES

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Aspirin, Hydrochloric Acid and Gastric Mucosal Microcirculation

Kittahore T, Guth PH (Research and Medical Services, VA Wadsworth Medical Center and UCLA Section of Medicine and The Center for Ulcer Research and Education, Los Angeles, California, USA). Effect of aspirin plus hydrochloric acid on the gastric mucosal microcirculation. Gastroenterology 1987; 98: 810-7.

Although aspirin is known to cause gastric mucosal injury, the pathogenesis of this damage is not clear. Efforts to elucidate the mechanism of gastric mucosal blood flow have been studied using different techniques, and conflicting results have been reported. In the present study, the authors studied the effect of topical application of aspirin and hydrochloric acid on gastric mucosal blood flow in rats, using in vivo microscopy to observe directly any changes in the superficial mucosal circulation. Ten minutes after the topical application of 20 mM aspirin in 50 mM HCl, the flow of red blood cells ceased and there were no longer present in the superficial mucosal microvessels in 76.8% (±7.7) of the microscopic field. Hydrochloric acid alone caused this effect in only 12.8% (±12.8) of the field, whereas aspirin alone had no effect. Along with this, white thrombi were seen flowing through mucosal microvessels. Mucosal hemorrhages developed subsequently in areas where mucosal flow had ceased initially. High concentrations of HCl were considered responsible for thrombus formation while low concentrations caused submucosal arteriolar constriction. These observations suggest that aspirin induced acid back-diffusion causes thrombus formation in mucosal microvessels and submucosal arteriolar constriction, resulting in cessation of mucosal blood flow, mucosal injury and focal hemorrhages.

Comment: It is well-established that aspirin causes gastric mucosal damage. The exact mechanism of mucosal injury is not known and various factors are suggested to include direct cellular damage (Ann J Dig Dis 1976; 21: 155-64), increased gastric acid secretion (Ann J Dig Dis 1973; 18: 225-37) and mucosal ischemia (Surgery 1981; 89: 337-41). Whatever the mechanism(s), the presence of acid in the stomach is considered essential for this damage. The effect on mucosal blood circulation has been studied extensively. In contrast to the accepted theory of the role of ischemia, some workers have reported an increase in the gastric mucosal blood flow (Gastroenterology 1970; 58: 31-39). Gastroenterology 1978; 77: 736-44). However, the techniques employed and the observations in these studies have been criticized (Gut 1983; 24: 340). As a consequence, it is possible that hemorrhages due to increased gastric blood flow occur as a compensatory phenomenon in the surrounding areas (Surgery 1975; 77: 86-93, Ann J Surg 1983; 149: 53-9).

The present study supports the ischemia theory. Blood flow cessation was due to submucosal arteriolar constriction and thrombus formation in post-capillary vessels. That the thrombus formation is mediated by HCl and not by aspirin alone supports the earlier observations that acid is essential for aspirin to produce mucosal damage, leading to the presence of acid in the submucosa in sufficient quantity. The role of aspirin lies in the disruption of the gastric mucosal barrier.

The cessation of blood flow is maximum at areas distant from collecting venules; this is probably so because of the slow velocity of blood flow in the capillaries, and the inability of slow blood circulation to neutralize, dilute and carry away enough of the back-diffusing acid. The observation that the mucosal haemorrhages occurred in the areas where superficial mucosal blood flow was absent has been attributed to hypoxia or induced damage to the capillaries in these areas. When reperfusion of mucosal capillaries occurs, the renewed blood flow or a burst of oxygen-derived free radical formation causes rupture of the weak capillary wall damaged by anoxia.

This study is unique in that it is possibly the first to try to correlate the mucosal changes induced by aspirin with vascular changes.

A New Concept in the Management of Variceal Bleeding?

Musta N, Grando L, Bosch J, et al (Hepatic Hemodynamic Laboratory, Liver Unit and Department of Surgery, Hospital Clinic I Provincial, University of Barcelona, School of Medicine, Barcelona, Spain). Effects of metoclopramide and domperidone on azgos venous blood flow in patients with cirrhosis and portal hypertension. Hepatology 1986; 6: 1244-7.

The effects of pharmacological manipulation of the lower oesophageal sphincter (LES) pressure on the oesophageal circulation in patients with cirrhosis and portal hypertension were investigated in 33 patients by measuring the azgos venous blood flow, which is an index of blood flow through oesophageal varicose and peri-oesophageal collaterals draining into the azgos venous system. Measurements were performed basally and after the blind administration of metoclopramide (20 mg iv; 12 patients), domperidone (10 mg iv; 12 patients) and placebo (9 patients). Both metoclopramide and domperidone caused a significant reduction in azgos blood flow, which decreased by 11.5% (p<0.01) and 15.6% (p<0.02) respectively. No significant change was observed in the blood flow of patients receiving placebo. Reduction of azgos blood flow represents a selective effect of metoclopramide and domperidone on the oesophageal circulation, since portal pressure, hepatic blood flow, cardiac output, heart rate and arterial blood pressure were unchanged. These results indicate that drugs which increase LES pressure may reduce the inflow of blood into the oesophageal varices in cirrhotic patients with portal hypertension.
Comment: The Spanish group needs to be congratulated for giving a new lease of life to pharmacology of portal hypertension by using drugs which selectively influence the oesophageal collateral circulation, an area gaining importance in recent years. An accurate estimation of blood flow through gastro-oesophageal collaterals and oesophageal varices obtained in the duodenal venous system is possible through a continuous thermal dilution technique (Hepatology 1984; 4: 424-8). Techniques for indirect (Ann Surg 1982; 143: 212-4) and direct (Gut 1987; 28: 234-6) measurement of intravascular pressures have also been available. However, the significance and correlation of intravascular pressure, oesophageal collateral blood flow and variceal bleeding is still far from clear.

While vasoactive drugs like vasopressin, somatostatin (Gastroenterology 1981; 85: 318-25) and propranolol (Hepatology 1984; 4: 1203-4) are known to decrease the oesophageal blood flow, these drugs have significant effects on systemic and pulmonary hemodynamics also. Mostil et al undertook a new approach in manipulating LES pressure to selectively influence the oesophageal collateral blood flow. Administration of metopropranolol or a dopamine agonist achieved significant reduction in oesophageal blood flow. The study has raised a number of issues for the future: (i) the development of techniques, especially non-invasive ones, for the independent study of oesophageal and peri-oesophageal collateral blood flow; (ii) a search for drugs selectively influencing oesophageal collateral circulation; (iii) controlled clinical trials to assess the efficacy of drugs increasing LES pressure in the management of variceal bleeding. The battlefield seems to be shifting from the portal to the systemic avenues.

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Resistance to Nalidixic Acid in Shigella dysenteriae Type 1—Another Mechanism


Shigella isolates were cultured from fecal specimens of patients with diarrhoea. Every isolate of S. dysenteriae type 1 and every isolate of S. flexneri were tested for their antibiotic sensitivities. Chemotherapeutic agents tested routinely were sulphadiazine, streptomycin, tetracycline, chloramphenicol, ampicillin, co-trimoxazole and nalidixic acid, and mecillinam in selected isolates. Nalidixic acid resistant strains were first isolated in May 1986 and by January 1987 they outnumbered the sensitive strains. All the nalidixic acid resistant strains were resistant to other antibiotics except mecillinam. The minimum inhibitory concentration (MIC) was >200 µg/ml for the nalidixic acid resistant strains and <3 µg/ml for nalidixic acid sensitive strains. Plasmid analysis of the nalidixic acid resistant strains revealed the presence of a 20 megadalton plasmid which was not detected in any of the sensitive isolates. Conjugation experiments using E. coli K12 strain and S. dysenteriae type 1 showed the transfer of the 20 megadalton plasmid to E. coli. The MIC for nalidixic acid for these exconjugants (>200 µg/ml) was similar to that of S. dysenteriae type 1. Spontaneous resistant mutants of S. dysenteriae type 1 were isolated at a frequency of about 5 × 10^-6. These resistant mutants lacked the 20 megadalton plasmid and the MIC for nalidixic acid of these derivatives was 25 µg/ml. Nalidixic acid resistant isolates developed resistance to mecillinam and co-trimoxazole at a frequency of 10^-4 and 10^-6 respectively.

Comment: In the recent past, epidemics of shigellosis in various parts of the world have been caused by organisms resistant to multiple antibiotics. Drug resistance has been increasing with the passage of time and from place to place. Resistance to nalidixic acid in S. dysenteriae type 1 was described from Kashmir (Lancet 1983; ii: 761). While in West Bengal the strains continued to be sensitive to this drug (Lancet 1984; 1: 162). In an epidemic in the UAE, the shigellae were sensitive to nalidixic acid (Lancet 1983; ii: 1291). The epidemiology of drug-resistance suggests that resistance may be transferable between bacteria (Bact Rev 1963; 27: 87). Multiple drug-resistant S. dysenteriae type 1 in Central Africa carried plasmids of compatibility group X (Lancet 1983; ii: 1075-6), while in Central America and South-East Asia, the drug-resistance was mediated by plasmids of compatibility group A (Lancet 1983; ii: 1074-6). In contrast to the plasmid-mediated nalidixic acid resistance in the present study, chromosomally mediated nalidixic acid resistance was demonstrated in the Kashmir study (Lancet 1983; ii: 761).

The observations of the present study have obvious therapeutic implications. Previously, nalidixic acid was considered as the drug of choice to treat 'resistant' strains and resistance to this agent was thought to be very rare. Not only is nalidixic acid considered effective and safe, its easy availability even in the developing countries is a major advantage. Alternative drugs are few and costly. Mecillinam is known to be quite effective against Shigella (J Infect Dis 1984; 150: 643-9) and may be used for the treatment of nalidixic acid resistant strains, but is expensive. The newer quinolones also have been found to be clinically effective against Shigella (Antimicrob Ag Chemother 1983; 27: 1772-8). Because of the high drug levels in the intestine, development of resistance should not be a problem. By avoiding the bactericides, clostridial species and streptococci, the problem of clostridial septicemia is less likely to occur with their use. Gentamicin has also been found to be effective in vitro, but in one clinical study antibiotics-coupled were not effective in the treatment of shigellosis (J Pediatr 1986; 72: 706-21). It seems that with the possibility of improved availability of the newer quinolones in the near future, these may well prove to be drugs of choice for treatment of severe infections due to nalidixic acid resistant strains. Besides drug treatment, personal hygiene, sanitation and general education on the preservative agents need to be stressed as these measures are effective in decreasing the spread of disease regardless of whether the shigellosis are sensitive or resistant to antibiotics.

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Vagal Cholinergic Control of Gastric Alkaline Secretion


Bicarbonate secretion by gastric mucosa is an important component of gastric mucosal defence. Both fundic and antral gastric mucosa have been shown to secrete alkali by an active transport process and the magnitude of this alkalinization is about 5-10% of maximal acid output. In the present...
study, the authors studied the gastric alkaline secretion in ranitidine treated healthy subjects and duodenal ulcer (DU) patients by using a gastric perfusion-aspiration system. A double lumen gastroduodenal Drelling tube with endotracheal cuff was passed and positioned under fluoroscopic control with the cuff inflated just distal to the pylorus to prevent any escape of gastric perfusate into the duodenum or any reflux of the duodenal contents into the stomach. The tube with openings located in the distal portion of the stomach was used to continuously aspirate gastric contents. Another polyethylene catheter attached to the tube with openings in the proximal part of stomach was used to perfuse the stomach with saline (pH adjusted to 6) containing phenol red as a non-absorbable marker. The HCO₃⁻ content was determined by back titration of the gastric perfusate to its original pH. Basal alkaline secretion showed periodic fluctuations, reaching peaks at phase III of the migrating motor complex in the stomach. Mean basal alkaline secretion in healthy normals and DU patients averaged 1120±142 and 880±72 μmol/l, respectively, and no correlation was found between basal and maximally stimulated gastric acid and alkaline secretion. Modified sham feeding in normal subjects and in DU patients increased this secretion to the peaks of about 28% and 36% of the maximal alkaline response to intragastric application of 16, 16 dimethyl PGE₂ in these subjects. Vagotomy did not significantly affect basal alkaline secretion but prevented the rise in alkaline secretion induced by modified sham feeding. Atropine decreased basal, and prevented the modified sham feeding induced, alkaline secretion. Pirenzepine had little influence on basal, and did not affect the modified sham feeding induced, alkaline secretion. The authors conclude that basal gastric alkaline secretion (i) fluctuates in phase with gastric motor activity, (ii) is similar in normal subjects and DU patients, and (iii) is markedly enhanced by vagal stimulation and this effect is abolished by vagotomy and atropine. Pirenzepine does not abolish this effect, suggesting thereby that M2 and not M1 subtypes of muscarinic receptors are involved in this stimulation.

Comment: Over 100 years ago, a Danish physiologist, Schierbeck observed an increase in canine gastric CO₂ after food ingestion (Scand Arch Physiol 1882; 2: 427-73). Subsequently, there was very little work in this area and it is only in the last decade that gastric bicarbonate secretion has become a subject of great interest. The fact that gastroduodenal mucosa secretes bicarbonate in various species including man has been well-established (Am J Physiol 1984; 246 G: 139-54, Am J Physiol 1985; 248 G: 188-91). However, the underlying mechanism and factors which control this secretion are not well-understood. The present study reveals some interesting observations. The alkaline secretion showed cyclic fluctuations, reaching its peak at phase III of the migrating motor complex in the stomach. Such fluctuations in gastric acid secretion are known but this kind of relationship between gastric motility and HCO₃⁻ secretion has not been described earlier. Furthermore, these authors found that HCO₃⁻ secretion in normals and DU patients was similar and there was no correlation between the basal or maximal HCO₃⁻ and H⁺ secretion. HCO₃⁻ secretion in DU patients has been reported normal (Gastroenterology 1985; 88: 1205-6) as well as low (Gastroenterology 1985; 90: 1472) compared with healthy subjects. The reason for this discrepancy is not clear. It is tempting to speculate that impaired HCO₃⁻ secretion may have a role in the pathophysiology of at least a sub-group of DU patients.

As atropine was shown to decrease the basal alkaline secretion in the present study, cholinergic drive seems an important factor in HCO₃⁻ secretion. The marked rise in secretion after sham feeding suggests that vagal nerves have a potent stimulatory influence. The precise mechanism for this rise remains uncertain. Sham feeding stimulates the release of gastrin and pancreatic polypeptide and these hormones are known to stimulate HCO₃⁻ secretion in dogs (Am J Physiol 1985; 248 G: 687-91). In the present study in humans, however, these hormones did not have any influence on HCO₃⁻ secretion. The gastric cholinergic stimulation was associated with a significant increase in intragastric release of PGE₂. However, as the stimulating effect of PGE₂ was not affected by vagotomy and atropine, it is likely that PGE₂ is involved in gastric alkaline secretion induced by vagal cholinergic stimulation.

Another point of interest is that the levels of basal bicarbonate secretion in the present study are about twice those reported in an earlier study (Gastroenterology 1985; 79: 581-6). How do we explain this difference? The authors of the present study have used the method of single back titration of gastric perfusate to its original pH. Complete inhibition of acid secretion by ranitidine and the occlusion of the duodenal bulb with an inflated cuff resulted in favourable conditions for complete recovery of HCO₃⁻ without any conversion to CO₂. In the other study, HCO₃⁻ output was calculated from intragastric pH and pCO₂ using the Henderson-Hasselbalch equation. In this method, it is presumed that CO₂ in the stomach lumen originates from the neutralisation of secreted HCO₃⁻ by H⁺. If there is diffusion or escape of CO₂ from the lumen of the stomach, it would give rise to false low values of HCO₃⁻ secretion (Gastroenterology 1985; 88: 2900-1). The different values in the two reports are thus most likely due to different techniques used for calculating the HCO₃⁻ output.

The role of bicarbonate as a protective agent has certain limitations: (i) it is essentially an alkaline barrier and is unlikely to provide resistance to offending agents other than acid; and (ii) the localization of peptic ulcer to certain areas suggests that there is localised defect in mucosal resistance which may not be related to bicarbonate secretion. (ii) high acid concentrations may easily overpower this barrier. Despite these limitations, bicarbonate secretion might be considered a first line defense, although not the only one.

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