GUEST EDITORIALS

ERADICATION OF GASTRIC HELICOBACTER PYLORI: ARE WE GETTING THERE?

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In 1984 Marshall and Warren discovered and isolated a curved bacillus living in the stomach of patients with gastritis and peptic ulceration[1]. Subsequent workers[2] demonstrated that they could induce persistent gastritis by ingesting the bacillus which had been up till then regarded as a commensal living in areas of gastric mucosal damage. Over the following decade, this organism named as Helicobacter Pylori (HP), has been shown to play a major role in the causation of duodenal ulcers. Benign ulcers appearing in stomachs which have not been exposed to non-steroidal anti-inflammatory drugs have also been strongly associated with gastric HP colonisation. HP has also been implicated in the aetiology of non-ulcer dyspepsia, gastric carcinoma and primary gastric lymphoma.

Amongst these diseases, the most challenging problem in the last decade has been that of duodenal ulcer recurrence after initial healing by modern H_2 Blocker drugs such as Ranitidine. This phenomenon is now largely attributed to coexisting colonisation of the stomach by H P[3]. The incidence of duodenal ulcer recurrence can be dramatically reduced if co-existing HP is successfully eradicated[4]. The recent consensus that HP-associated duodenal ulcer should be treated by HP eradication will probably be extended to HP-associated gastric ulcer in the near future. However, the potential benefit of eradication of HP in populations at high risk of gastric cancer has not yet been properly addressed.

This spiral-shaped gram-negative rod has carved out for itself a unique ecological niche in or near the unstirred mucous layer lining the gastric surface and pits. This remarkable evolution has been achieved by acquiring the capacity to buffer lethal gastric acid with ammonia (produced in the bacillus by the action of urease on urea)[5]. Although the ecology of the organism has not yet been studied in detail, many publications have shown that HP establishes itself in the gastric antrum in preference to the gastric body[6]. The much greater acid-producing activity in the gastric body suggests that mechanisms protecting HP against attack by gastric acid are not yet completely evolved.

Colonisation of the gastric antrum stimulates the antral "G" cells to release an enterohormone called gastrin which in turn leads to excess production of acid by the gastric parietal cells. This hyperchlorhydria is believed to be one of the mechanisms by which H P produces duodenal ulceration. Hyperchlorhydria causes areas of gastric metaplasia[7] to appear in the duodenum which are soon colonised by more HP organisms.

This vicious circle can be broken by administering antimicrobials selected on the basis of invitro sensitivities of the organism and on their ability to heal HP-associated gastritis. Because of the ease with which resistant strains of HP emerge, triple therapy (bismuth subcitrate, amoxycillin and metronidazole) continues to be the most popular regimen. Endoscopic studies of DU patients using multiple gastric biopsies have shown that DU healing and short term eradication can be achieved in over 85% of patients[8]. In such patients, the incidence of recurrence of HP in repeat gastric biopsies one year later is typically 50% [9,10]. Duodenal ulcer recurrences are confined almost exclusively to those patients in whom HP persists in the gastric mucosa[11].

Persistence of HP, with its attendant risks of chronic duodenal ulcer, has been partly attributed to reinfection of the stomach. This is possible especially where sanitary conditions are poor[12] ,

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in overcrowded areas[13], in paediatric institutions[14], and in endoscopy units if equipment is not adequately decontaminated.

However, most failures of eradication of HP infections are thought to be due to incomplete antimicrobial action. This may result from poor drug compliance or from primary drug resistance. The large number of tablets prescribed in the triple therapy regimen increases the frequency of side effects and reduces compliance. Primary resistance to one or more of the antibiotics may precede the treatment especially in females who were prescribed metronidazole previously for pelvic inflammatory disease. The efficacy of these antibiotics is likely to be limited by the fact that key metabolic pathways in the bacterium that could be targeted by antimicrobials have not yet been elucidated in detail. In addition to its habitat in the gastric mucous, HP has been found inside gastric mucosal cells[15]. This could further decrease its susceptibility to antibiotics.

Recent developments in the field of duodenal ulcer therapy have raised the hopes that this therapeutic hurdle can now be overcome by an alternative approach. There have been several recent trials[16, 17] in which a single antimicrobial (amoxycillin up to 3 grams daily) was combined with a potent gastric acid suppressor (Omeprazole up to 60 mg daily). These regimens achieved eradication rates of 80 to 90% which are similar to those obtained using triple antibiotic therapy. It is logical to postulate that an organism which has specialised and evolved in such a way as to flourish in acid conditions will fare badly when these conditions are suddenly removed by potent acid suppression. Indeed the addition of Omeprazole drastically reduces the minimum inhibitory concentration of amoxycillin on HP in vivo. It has been suggested that when acid is suddenly abolished much of the ammonia it produces accumulates intracellularly as this remains unbufferred; the organism dying in a suicidal act of self poisoning!

Hopes of effective long term eradication have been raised by a recent report of a pilot study[18] of a seven-day regimen which combines Omeprazole (20 mg daily), low dose Clarithromycin (250 mg twice daily) and Tinidazole (500 mg twice daily). Clarithromycin is the only antimicrobial effective against HP in vivo when used as a single agent. This is the first regimen to achieve 100% eradication of H Pylori.

If these exciting results are reproduced by further studies in the course of 1995, a decade of research into HP behaviour will have resulted in a potent tool for its eradication. This anticipated breakthrough will hopefully be complemented in the future by the development of an oral vaccine which will enable large-scale immunisation of children in endemic areas with the aim of reducing the incidence of carcinoma of the stomach in adulthood[19]. Effective immunisation has already been achieved in mice against murine strains of Helicobacter by prior oral administration of disrupted whole cells of these organisms[20].

Notwithstanding his ingenuity and his successes in combating this unusual organism, man must remain vigilant, respecting this microbe's ability to adapt to the changing habitat of the stomach with relative ease. Already there are theoretical fears that the organism may assume coccoid forms similar to those found in drinking water, so as to survive in adverse conditions. Hopes of universal eradication of gastric HP, cannot be considered before the ecology of this organism has been further elucidated.

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