

No longer a pain in the gut — how Tagamet led peptic ulcer treatments

In the third article in a series on landmark drugs, Jenny Bryan retells the dramatic effect that Tagamet had on millions of peptic ulcer sufferers

If one Googles Tagamania today the search engine will come up with sites featuring an American piebald horse of illustrious pedigree. But 30 years ago, you would not have needed Google to know that Tagamania referred to the huge commercial success of the breakthrough peptic ulcer treatment, Tagamet (cimetidine). The drug transformed the fortunes of Smith, Kline and French (SKF) — a US company with a pre-eminence in psychotropics which was being eroded by Swiss giant, Hoffman La Roche. The drug had a dramatic impact on the lives of millions of people with peptic ulcer disease.

“Before Tagamet, the only options were antacids or surgery. You needed to drink about 8L a month of antacids to get a better effect than placebo and you only offered people surgery when they were in so much pain that they wouldn’t mind the dumping [of food into the intestine before it has been broken down in the stomach], sweating and diarrhoea, which followed vagotomy with or without removal of the antrum,” recalls Roy Pounder, Emeritus Professor of Medicine, University of London. “Ironically, there had just been improvements to make vagotomy highly selective, with less risk of side effects. But the operation was very demanding and, if it didn’t work, the ulcers came back,” he added.

Tagamet was launched in the UK in November 1976 as the first histamine (H₂) antagonist. It emerged from a research programme started at SKF in 1964 when Sir James Black joined the company from ICI, fresh from his success with beta blockers.¹ Antihistamines had been available for the treatment of allergic reactions since the 1940s but they did not block the action of histamine in all tissues. For example, they had no effect on histamine-mediated release of gastric acid from the parietal cells of the stomach.

In 1966, it was proposed that there were two histamine receptors — H₁, antagonised by antihistamines such as mepyramine, and non-H₁, which were not.² SKF scientists therefore set about developing compounds that were structurally similar to histamine (unlike the antihistamines marketed at that time for allergies) and would compete with histamine at non-H₁ receptors.

In the first four years of the programme around 200 compounds were synthesised, but none showed any evidence of antagonism at non-H₁ receptors.¹ After much chemical manipulation, a competitive antagonist of histamine in non-H₁ tissue systems was developed, called burimamide, and classified as an H₂ receptor antagonist.³

Unfortunately, it was not active enough in human studies and a second H₂ antagonist, called metiamide, was synthesised. This was considerably more potent than burimamide and reduced excessive gastric acid secretion in human studies. In initial trials, there were significant reductions in pain and antacid consumption compared with placebo, and improved ulcer healing,^{4,5} but the use of metiamide was limited by reversible granulocytopenia in a small number of patients.

It was third-time lucky for SKF with the result of a final session in the chemistry laboratories being cimetidine. It inhibited gastric acid, passed toxicity tests and, in doses of 0.8–2g per day over three to four weeks, achieved 70 per cent ulcer healing rates.⁶

Major impact

“The first dose of Tagamet was the best because patients felt so much better when they started taking it. You did not need to be a gastroenterologist to prescribe Tagamet and when it was launched every doctor wanted to hear about it because they all had patients with dyspepsia whether they were gastroenterologists, orthopaedic surgeons or gynaecologists,” Professor Pounder explains.

Within weeks of its launch, Tagamet was having a major impact on ulcer disease, but it was no cure. Within six months of stopping treatment, 80 per cent of patients relapsed but maintenance studies soon showed that this could be reduced to less than 30 per cent with low-dose cimetidine.⁷ Before long, it was proposed that patients who responded to an initial course of treatment should follow this with maintenance therapy for six to 12 months and, depending on how soon they relapsed after this, have a further course of cimetidine or consider surgery.

Doctors were wary of putting patients on prolonged maintenance therapy in case of long-term toxicity and these concerns were fuelled by studies emerging at the end of the

The discovery that will revolutionise the treatment of peptic ulcers and associated gastrointestinal disorders

Complete healing or marked improvement of duodenal ulceration has frequently been obtained within 8 weeks. Early symptomatic relief is normally achieved in patients receiving Tagamet treatment. Furthermore, Tagamet is well tolerated with minimal side effects which, together with its convenient dosage, means Tagamet is well suited to everyday treatment.

Presentations
Tagamet (cimetidine) is available as 200 mg film-coated tablets engraved TAGAMET/SKF & F 200, available in containers of 100 (E4.28) and 500. Tagamet is also available as orange coloured, peach flavoured syrup (200 mg/5 ml) in bottles of 200 ml (E6.28), and as 200 mg/2 ml ampoules for i.v. use.

The discovery
Until recently, one aspect of gastric physiology remained paradoxical — histamine was known to be a potent stimulant of gastric acid, yet conventional antihistamines were totally inactive in this area. Confronted by this apparent anomaly investigators began to suspect that there might in fact be two types of receptor sites for histamine — one mainly for allergic reactions (H₁) and the second for gastric acid secretion (H₂). In 1964, the SKF & F research team set out to find a new class of therapeutic agent by chemical modification of the histamine molecule. They were seeking an agent capable of blocking the action of histamine at the H₂ receptor site. After 12 years of extensive research, this search has resulted in the development of Tagamet, the H₂ receptor antagonist, with the fundamental property of controlling gastric acid secretion.¹

A real breakthrough
Due to its dramatic reduction of gastric acid secretion Tagamet has achieved quite remarkable results in peptic ulcers and associated gastrointestinal disorders.

Complete healing of duodenal and gastric ulcers^{1,2,3,4,5,6} (proved endoscopically) is seen in most patients after 4 weeks' treatment.

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SK&F
The H₂ receptor antagonist
A British Discovery

Tagamet — an advertisement in *The Journal* in 1977

1970s, which raised the spectre of stomach cancer. Low or absent levels of stomach acid were associated with bacterial overgrowth in the stomach and resulting bacterial conversion of exogenous nitrates to nitrites, leading, potentially, to the synthesis of carcinogenic N-nitrosamines.⁸ Increases in nitrites and N-nitrosamines were reported with cimetidine treatment,⁸ and controversial extrapolations to stomach cancer were made, although never subsequently confirmed.

Despite the rumbling safety debate about cimetidine, there was immense interest among other pharmaceutical companies in developing rival H₂ antagonists. The reasons were obvious. In the UK alone, over a million patients were treated with Tagamet in the first five years after its launch.

Annual worldwide sales reached £150 million within two years of launch and around £300 million at the start of the 1980s. Before long, SKF was able to take over UK pharmaceutical company, Beecham, the name of which was synonymous with cough and cold remedies. But Smith Kline Beecham (SKB)

was, in turn, swallowed up by Glaxo, thanks partly to the profits it made from the second H₂ antagonist, ranitidine (Zantac), which was launched in 1981 and went on to eclipse even Tagamet — becoming the world's best-selling drug five years later.

Professor Pounder believes that the key to Zantac's success — aside from the textbook marketing operation — was its easier dosing regimen compared with Tagamet and its lack of drug interactions. "Tagamet had to be taken four times a day, but when Glaxo tested Zantac taken twice a day, the results were at least as good, partly because of the better compliance. So they launched using a twice daily regimen," he explains.

Cimetidine (Tagamet) is an inhibitor of cytochrome p450 and interacts with a wide range of commonly used medicines, including some antiepileptic and anticoagulant drugs, so that dose changes are needed. It is also associated with male sexual dysfunction — another feature which it does not share with ranitidine.

The final nail in the coffin for Tagamet came with two large multicentre, head-to-head trials of night-time maintenance therapy that showed a 12-month relapse rate of 16–23 per cent for those taking Zantac compared with 37–43 per cent for those on Tagamet.^{9,10}

"British doctors were quite conservative about switching to Zantac, and Tagamet was invented in Britain, even though SKF was an

American company. But the combination of a slightly better product and a more aggressive marketing campaign finally won the British over to Zantac," says Professor Pounder.

The last challengers to enter the H₂ antagonist market were famotidine (Pepcid PM) from Merck Sharp & Dohme Limited and nizatidine (Axid) from Lilly, both of which were launched in 1988 — over a decade after Tagamet's original breakthrough. They offered comparable ulcer healing rates to cimetidine and ranitidine, but without the drug interactions of cimetidine. Because they were priced at the higher level of Zantac, rather than the cheaper Tagamet, doctors were advised to stick with the products they already had.¹¹

However, MSD did manage to steal ahead of its more established rivals in getting Pepcid AC on to the over-the-counter market for heartburn and dyspepsia six weeks ahead of SKB's Tagamet 100 in 1994 and over a year ahead of Glaxo's Zantac 75.

But the ink was barely dry on the licences of famotidine and nizatidine before the first proton-pump inhibitor burst on to the scene, promising even greater, more prolonged stomach-acid reduction than could be achieved with the H₂ antagonists. And, with the patents expiring on the drugs that had transformed two nice but dull companies into giants of the pharmaceutical industry, life moved on in the world of ulcer disease.

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