

## Leading article

# 1976 and all that! – 20 years of antisecretory therapy

The introduction of cimetidine (Tagamet) by Smith, Kline & French (now SKB) in 1976 is a landmark event in the history of therapeutics. The drug heralded a revolution in the treatment of acid-peptic disorders, initiated an era of intense research and discovery benefiting all of gastroenterology, and resulted in unprecedented expansion of the pharmaceutical industry. A voluminous literature exists relating to the discovery, development, and use of cimetidine itself, and to the various other antiulcer drugs that have followed in its wake.<sup>1-3</sup> What then are the landmarks during a period of two decades when cimetidine became the first billion dollar drug and antiulcer agents have exclusively occupied the position of the World's top selling drug?

### H<sub>2</sub> antagonists after cimetidine

The cycle of breakthrough discovery followed by line extension is a fundamental characteristic of consumer products, including drugs. In the case of pharmaceutical industry, what are commonly, but rather unfairly, referred to as 'me-too drugs' provides the basis for refining a particular therapeutic class with respect to pharmacodynamics, pharmacokinetics, side effects, and patient tolerability. Ranitidine<sup>4</sup> was introduced by Glaxo in 1981 as a more potent drug with a superior side effect profile and, backed by a skillful marketing campaign, superseded cimetidine as the world's most successful drug. Famotidine,<sup>5</sup> synthesised by Yamanouchi, was the third H<sub>2</sub> antagonist to be registered and this remains the most potent agent available for clinical use. Although nizatidine,<sup>6</sup> the fourth H<sub>2</sub> antagonist to be marketed worldwide, does not represent a therapeutic advance as such, the pricing policy adopted by Lilly has resulted in substantial sales exceeding half a million dollars per year and inclusion of the drug on many hospital formularies.

The price of success can be readily measured by sales figures and in this regard, the four H<sub>2</sub> antagonists available in the USA (the world's largest market) had combined sales of \$3.5 billion last year. However, what of the failures? Since cimetidine, about 30 H<sub>2</sub> antagonists have been investigated in humans but only five have been marketed with roxatidine available in only a few countries. This high attrition rate largely reflects the extreme safety and efficacy of the H<sub>2</sub> antagonists used clinically, with toxicity (for example, osmetidine<sup>7</sup>) or lack of therapeutic advantage (for example, etintidine<sup>8</sup>) being the principal reasons for discontinuing drug development programmes.

Toxicity findings with the H<sub>2</sub> antagonist tiotidine first drew attention to the ability of antisecretory agents to induce gastric mucosal changes such as glandular dilatation and hyperplasia, and of the need to systematically examine the entire stomach.<sup>9</sup> In addition, well publicised lesions of the dysplasia-carcinoma complex were observed in 17 of 828 rats receiving this compound during the course of long term dosing studies. As tiotidine is a chimeric structure consisting of the cimetidine side

chain and the thiazole ring common to famotidine (which results in a reversible antagonist of intermediate potency), it is difficult to conceive of an explanation for the appearance of adenocarcinoma based on structure activity.<sup>10</sup> Inexplicable gastric toxicity also befell the SKB compound lupitidine, which caused hyperplasia in the fore-stomach of the rat.<sup>11</sup>

The profile of the H<sub>2</sub> antagonist sector emerging in the early 1980s conformed to the model that major markets can support four or five related drugs after which the return on development costs make further introductions commercially unattractive. In an attempt to radically change the profile of reversible antagonists, many companies sought to develop long acting inhibitors, either through an increase in half life or by non-competitive/irreversible interaction with the receptor, to increase the duration of antisecretory cover. While this search went on, the pattern of use of marketed H<sub>2</sub> antagonists was also changing because it was found that a single night time dose was as effective as multiple daily doses, at least in duodenal ulceration. It was also clear that existing compounds lacked efficacy in oesophageal ulceration. In contrast, many non-competitive H<sub>2</sub> antagonists were extremely potent and displayed a prolonged duration of action in vivo at sub-maximal doses. For example, the most potent of these compounds ICI 162,846 showed pronounced antisecretory activity in humans 24 hours after dosing at 1-5 mg.<sup>12</sup> The other major factor in trying to market these compounds lay in counteracting the commercial threat posed by development of proton pump inhibitors (PPIs).

Both SKB (lupitidine) and Glaxo (lamptidine and loxidine) were successful in taking long acting H<sub>2</sub> antagonists into clinical trials. However, development of these compounds was stopped because of the occurrence of carcinoid lesions in rat long term toxicity studies. Loxidine in particular was withdrawn from development amid considerable publicity.<sup>13</sup> Adverse press in relation to target organ toxicity undoubtedly delayed the development and ultimate approval of the first PPI omeprazole.<sup>14</sup> In what became a highly commendable stance, Astra set about explaining the scientific basis of these lesions. Not only did this work facilitate regulatory approval of omeprazole but also led to advances in understanding the trophic role of gastrin and the pathobiology of the enterochromaffin-like (ECL) cell.<sup>15 16</sup>

### Proton pump inhibitors

A year after the UK launch of cimetidine, the third in a series of International Symposia on Gastric Ion Transport took place in 1977 in Uppsala, Sweden.<sup>17</sup> After the demonstration of ATP driven, potassium dependent transport of protons by gastric vesicles in 1974,<sup>18</sup> five of the 40 papers at this symposium discussed properties of the gastric H/K-ATPase. A sixth from Hassle (now Astra) reported that a benzimidazole derivative H83/88, unlike metiamide, induced non-competitive inhibition of hista-

mine stimulated acid secretion from isolated gastric mucosa and inhibited secretion induced by the intracellular mediator cAMP.<sup>19</sup> While it was clear that this inhibitor had not been discovered through the systematic pharmacological analysis that had characterised discovery of cimetidine, history has shown the therapeutic impact of this class of antisecretory drugs to be just as significant.

Omeprazole (Losec) was launched by Astra in 1989 after a tortuous and somewhat acrimonious development programme. In contrast with cimetidine, the precise mechanism of action of the drug only emerged during the course of its development.<sup>20</sup> This in turn enabled rationalisation of the extremely high efficacy and specificity of benzimidazole derivatives. Thus accumulation of the basic pro-drug in the secretory canaliculus of the parietal cell is followed by acid conversion to reactive sulphenamides, which inactivate the H/K-ATPase by disulphide bonding to thiol groups in the extracellular domain of the enzyme.<sup>21</sup> The restricted location of H/K-ATPases and the uniquely acidic environment of the gastric enzyme, combined with the pK/log D of the compound itself, impart a degree of specificity rarely encountered in medicinal chemistry.

Although the development of omeprazole was characterised by a reluctance to emphasise its ability to induce prolonged acid suppression, clinical success of the drug is clearly a direct consequence of its powerful and sustained antisecretory action.<sup>22</sup> During clinical trials, omeprazole produced faster rates of ulcer healing and healed ulcers resistant to H<sub>2</sub> antagonists. Most significant, however, was the fact that omeprazole proved highly effective in moderate to severe reflux disease wherein the H<sub>2</sub> blockers lacked efficacy.<sup>23</sup> PPIs have also become the drugs of choice for combining with antibiotics to eradicate *Helicobacter pylori*, with Astra having set a precedent by gaining regulatory approval for the combination of omeprazole and an antibiotic. The success of cimetidine and ranitidine has now been emulated by omeprazole, which became the number one selling drug in Europe and third on the world list in 1994. Given that peak sales usually occur 10–12 years after launch, it is probable that the success of omeprazole will continue into the 21st century.

Pantoprazole<sup>24</sup> (Byk-Gulden) and lansoprazole,<sup>25</sup> licensed to various companies in the West by Takeda, are now available in many countries and a fourth PPI, rabeprazole is awaiting regulatory approval in Japan. Whether the world market can sustain a fourth example of this class of drug is questionable. A joint agreement between Eisai and Lilly to market rabeprazole in the West has recently been discontinued. Other approaches to inhibiting the gastric H/K-ATPase, principally via agents directed at the potassium binding site, which gives rise to reversible PPIs with a shorter duration of action, have been largely abandoned as they seem to offer no advantage over existing drugs. What then is likely to happen to the PPI market as greater experience is gained with use of the newer agents?

Differences between the available PPIs have been claimed with respect to interaction with both the H/K-ATPase and cytochrome P450 enzyme systems. In the case of the proton pump, differences have been reported with respect to the number of cysteine binding sites, their effects on conformation and partial reactivity of the enzyme, rates of acid activation and thus onset of action, kinetics of reversal by scavenger mechanisms, and antisecretory potency in animals.<sup>26, 27</sup> However, none of these differences would seem to have any significance for clinical efficacy because, at the recommended doses, antisecretory activity and ulcer healing rates are similar. PPIs are also capable

of killing *H. pylori* in vitro<sup>28</sup> but this property, at least as far as current drugs and formulations are concerned, is probably also irrelevant because the luminal concentrations achieved are negligible due to enteric coating. Whether lansoprazole or pantoprazole, if either, emerges as a clear second to omeprazole in the PPI sector rests on development strategy and safety issues such as selectivity/tolerability and metabolism. Safety in terms of freedom from drug interactions was a major determinant in establishing market share in the H<sub>2</sub> sector.

### Current issues and future therapy

Although ulcer recurrence was an identifiable shortcoming of antisecretory therapy, clinical needs seemed to have been largely met towards the end of the 1980s with the availability of ranitidine and omeprazole. However two separate findings, a reduction in the frequency of ulcer relapse in patients receiving bismuth therapy<sup>29</sup> and the discovery of an association between *Campylobacter pylori* infection and ulcer disease,<sup>30</sup> resulted in what could give rise to a third major therapeutic category of antiulcer treatment. A once daily monotherapy inducing reliable eradication of *H. pylori* would undoubtedly be a commercially attractive proposition,<sup>31</sup> It is, however, interesting to note that *H. pylori* was mentioned only twice among the replies we received from the 10 chief executive officers representing major drug companies with interests in antiulcer therapy to whom we wrote before preparing this leading article with the request to list, from their perspective, the three most important issues which currently affect this drug sector.

Certainly anti-*H. pylori* monotherapy is some considerable way off. Moreover, such treatments will not impact the need for antisecretory therapy in patients with reflux oesophagitis, those with peptic ulcer and associated reflux, or to counteract the gastrointestinal side effects of NSAIDs. There is also uncertainty concerning the role of *H. pylori* eradication in various other categories of ulcer patients, for example those who present with bleeding.<sup>32</sup> Further, there is scope to develop existing PPIs for other indications and for developing a new generation of PPIs to inhibit H<sup>+</sup> transport at other sites, for example the osteoclast, and hence target the massive post-menopausal and osteoporosis markets.

While eradication of *H. pylori* is beginning to take its place as a main line therapeutic approach in benign ulcer disease, opinions vary on the optimum antibiotic combination, dosing regimen and duration of treatment.<sup>33</sup> Indeed the fact that infections with bacilli such as brucella and tuberculin, which bear some comparison with *H. pylori* and are known to require long term treatment with a cocktail of antibiotics argues against a short course of a single agent. Vaccination seems to offer a promising approach to eradicating *H. pylori* unhindered by the prospect of multiple resistance. The joint venture between Oro Vax and PMSV to develop and market such products has already resulted in an urease based oral vaccine that stimulates a strong immune response in low doses, cures established infection in animals, and has just successfully completed Phase I clinical trials.<sup>34</sup> In addition to the potential for reducing the incidence of gastric cancer, vaccination could have a major impact in the developing world where almost the entire population is infected with *H. pylori* at an early age and which has hitherto suffered from being an unattractive market for the pharmaceutical industry.

Analogies have been drawn between therapeutic developments in the antiulcer and older antihypertensive markets.<sup>35</sup> Many of the current concerns in ulcer treatment

are also similar, including therapeutic equivalence and cost-benefit, specificity and side effects, long term tolerability and safety, as well as outright commercial issues such as market share, patent expiry, and generic competition. A major difference between the two, however, is the importance of self medication in treating acid-peptic disorders. Given that safety has been a prime factor in gaining regulatory approval for over the counter use of H<sub>2</sub> blockers, eventual appearance of PPIs in this sector cannot be ruled out.

In extending the analogy between ulcer disease and essential hypertension, where there are eight classes of antihypertensives in current use, it would be surprising if H<sub>2</sub> blockers and PPIs were the end of the story in treating acid-peptic disorders. There are no lack of clues on which to base a search for clinically relevant approaches, not least of which are the sensitivity of *H. pylori* to agents other than antibiotics or the ameliorating effect of the gravid state. In closing, however, we return to the original stimulus for this article, namely the 20 year anniversary of the launch of cimetidine. It is a sobering thought that with peak sales of \$200 million forecast before its launch, the antiulcer drug market has developed into a \$10 billion per year industry contributing some \$2 billion to the UK balance of payments. Perhaps it is most fitting, however, to close with a reminder of the name of the person responsible for initiating the whole story namely Sir James Black.<sup>36</sup>

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