THERAPY UPDATE

Which PPI?

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The world of drug development is inevitably that of "me toos". The successful new product is followed by its imitators. This became obvious when the first β blocking agent pronethalol was followed, from the same company, by the still widely used non-selective β blocker propranolol, and then by a range of other β blocking drugs with particular selectivities. These innovations were, broadly speaking, linked to improved targeting of receptors, hence leading to more precise pharmacodynamic profiling. The developments themselves were based on the prevailing state of the art knowledge of likely structural relationships between the designed molecule and the agonist whose actions were to be modulated. As that knowledge was imprecise, proof of potency depended on classical pharmacological studies in experimental animals or tissues.

In the four decades which have since passed, our understanding of molecular structures and receptor binding have improved enormously. Molecular design is now driven by combinatorial chemistry and computer modelling,[1] and the value of pharmacological studies more often lies in confirming compound activity rather than in determining its presence. Secondly, refinements of pharmacological understanding have allowed greater precision of agonist or antagonist functioning.

In gastroenterology these decades have seen the sequential development of the histamine H_2 receptor antagonists and the proton pump inhibitors (PPIs). It is therefore inevitable that drugs developed have become more potent, more targeted, and more similar. The clinician is now assured of being able to prescribe a highly effective drug for the purpose intended where worries about the possible long term effects of acid suppression have not so far proved justified.[2] Differences between PPIs have seemed therefore mainly to lie in accepted indications, potency, particular adverse effect profiles, and cost.

Differences in indications mainly reflect variations in those sought by individual companies, and potency may really reflect dose. Costs are broadly affected by patent protection, thus a new and innovative drug is likely to be relatively expensive, at least initially, because it is innovative and lacks competition. Its successors will be cheaper, as will copies of the initial innovation as generics. Positions will vary with market forces. In theory, they should also be susceptible to pressures from better or worse adverse effect profiles, and to greater or lesser acceptance of the innovative product as well understood and reliable.

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Prediction of safety relative to other compounds with the same agonist or antagonist profiles remains difficult. The accent in drug development is mainly on the activity of the compound in the desired area. Molecular designers will avoid compounds with structures which appear obviously likely to be toxic, but face the problem that hepatic, renal, skin, neurological, or other toxicity is hard to forecast where our knowledge of body function and dysfunction is still imperfect. Differences in potency, in essence, imply reductions or increases in dosages required to achieve desired effects. It would seem sensible to reduce doses (avoirdupois) of xenobiotics where possible, although the doses of drugs ordinarily employed, in the milligram range, are generally quite low.

Where does this place us with the PPIs? These are potent well targeted drugs, used in much the same doses. Taken overall it is to be expected that the outcome of treatment in common indications, and reflux oesophagitis is the exemplar, will be much the same for each. The indications for treatment vary. These differences must reflect indications sought as there is no intrinsic likelihood that the drugs differ.

Adverse effect profiles are difficult to compare because standard clinical trials where head to head comparisons are conducted are unlikely to include sufficient individuals to allow reliable conclusions. Relatively early in its marketing the use of omeprazole was associated with the occurrence of diarrhoea, headache, and skin rashes. These suggested adverse responses were probably rare, and acceptance of them depended on acceptance of adverse event reports in spontaneous reporting systems (where causality cannot be established with confidence). It is impossible to know whether they are likely to be more or less common with the more recently marketed compounds lansoprazole, pantoprazole, and rabeprazole.

All PPIs are removed, at least in part, through the cytochrome P450 system. Omeprazole has long been known to modestly impair removal of diazepam, phenytoin, and warfarin, while all PPIs may impair antifungal absorption and enhance plasma digoxin levels but the clinical effects may be insignificant.

Does the development of esomeprazole alter the conclusion of essential similarity between PPIs? The particular virtue of the drug is that it is not a racemate but contains only the S-isomer of omeprazole. As such it removes any risks associated with exposure to the less active, in acid suppressant terms, R-isomer, thus possibly reducing the likelihood of drug toxicity. However PPIs seem to have excellent short term safety profiles, and possibly (although evidence is fragmentary) good long term profiles. Hence additional benefits here may be limited.

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- All PPIs are potent, effective, and generally safe.
- Differences in treatment outcome differ little at equipotent doses.
- Accepted indications may nevertheless vary according to the evidence available and the licence sought.

Esomeprazole seems to be removed more slowly than omeprazole[3] so that a given dose would be expected to exert effects for longer. Direct milligram equivalent doses of (say) 20 mg of omeprazole and 20 mg of esomeprazole will therefore give more obvious control of acid secretion with the latter, probably because of 100% exposure to the S-isomer but possibly because its removal rate is relatively slow. How much of an advantage this may be if PPI doses are tailored to the level which gives symptom relief is uncertain.

Guidance from the National Institute of Clinical Excellence does not differentiate between PPIs except on the grounds of price and accepted indications.[4] It is hard not to agree with their advice which can be encapsulated as use the lowest effective dose of the cheapest drug for the shortest possible time. A recent review of the clinical pharmacological properties of the four standard PPIs omeprazole, lansoprazole, pantoprazole, and rabeprazole also concludes that they are essentially similar.[5]

PPIs stand out as potent, effective, and safe. Given the current facility with which molecular targeting can be achieved through computer simulation and prediction of structure-activity relationships, one is left asking just how innovative the construction of a me too molecule may now be? Perhaps not very.

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2 Yeomans ND, Dent J. Personal review: alarmist or legitimate concerns about longterm suppression of gastric acid secretion? *Aliment Pharmacol Ther* 2000;**14**:267–72.
3 Spencer CM, Faulds D. Esomeprazole. *Drugs* 2000;**60**:321–9.
4 *Guidance on the use of proton pump inhibitors in the treatment of dyspepsia*. NICE, UK: Technology Appraisal Guidance No 7, 2000 (www.NICE.org.uk).
5 Stedman CAM, Barclay ML. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *AlimentPharmacol Ther* 2000;**14**:963–78.