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Clinical research methods in gastroenterology

Marjorie M. Walker¹ & Brendan J. R. Whittle²

¹Faculty of Medicine, Imperial College London, St Mary's Campus, Norfolk Place, W2 1PG, and ²William Harvey Research Institute, Barts & The London, Queen Mary's School of Medicine, Charterhouse Square, London EC1M 6BQ, UK

Why publish this series on *clinical research methods in gastroenterology* now, when all of the key targets for research and development of new drugs in gastroenterology have presumably been achieved from a clinical pharmacologist's perspective? Well, as this innovative series of review articles will demonstrate, we are far from that the state of therapeutic Nirvana in this area. Moreover, evaluation of the side-effect profile of a range of new chemical entities on the gastrointestinal tract has become an issue of ever-increasing importance and more rigorous assessment in appropriately designed studies is becoming a necessity for several new classes of drug.

This series of 8 short reviews, which will appear at regular intervals in the *Journal*, discusses the areas of clinical need for new drug development in the gastrointestinal tract, working literally from top to bottom. Importantly, the papers give details of the methods available to both clinical pharmacologists and gastroenterologists for evaluating new drug entities and understanding how these novel agents may actually work in the clinical setting. Key topics such as the variability of the therapeutic response and hence the predictive power of the techniques and those factors that can reduce their specificity or sensitivity when used in drug development have been considered. In addition, the assessment of both minor and major side-effects has also been addressed.

Worldwide, developing effective and economical drugs for gastrointestinal disease remains an unfulfilled task for the pharmaceutical industry. A review of the burden of digestive disease in the USA estimated that direct annual costs for all digestive diseases were \$85.5 billion. The disorder with the highest annual direct costs in the United States was gastro-oesophageal reflux disease (GORD), estimated at a cost of some \$10 billion per annum in health care in the year 2000 [1].

Despite significant progress in the development of efficacious acid suppressives over the past 25 years, from histamine H₂-receptor antagonists to proton pump inhib-

itors, this area is still of major importance. Thus, the effective and economic control of the gastric acid load in GORD, peptic ulcer disease and dyspepsia that afflicts a great number of the population, is still a target for drug development, refinement and pharmaceutical modification. Moreover, changes in gastric function can affect the bio-availability of some medications, a factor that should be borne in mind by the clinical pharmacologist when designing pharmacodynamic and pharmacokinetic protocols. A review of this important area and the methods used to evaluate oesophageal and gastric function in the clinic, not only for the determination of the various secretions but also of gastric motility, is presented by Pohle and Domschke (pp. 156–164) in this current issue.

Helicobacter pylori infection of the stomach has a significant clinical outcome in about 30% of affected individuals, resulting in peptic ulcer, gastric cancer and in some rare cases, lymphoma [2]. Selection of appropriate patients needing eradication therapy is therefore of importance, but there are difficulties with compliance of patients with the established regimens and an identifiable increase in antibacterial resistance. Hence, the problems caused by this infection are still very much with us and research and development will have to meet the challenge of evaluating new therapies or drug combinations, as well as vaccines. Another factor of importance to clinical pharmacologists is that the local inflammation produced by this organism in the stomach can potentially alter drug absorption of a number of therapeutic agents in the gastric compartment. The paper by Goddard and Logan explores these difficulties in the clinical setting and also discusses the best methods for detection of the bacteria and assessment of eradication.

There are always associated risks in prescribing any drug, and this is exemplified by the commonly used non-steroidal anti-inflammatory drugs (NSAIDs). A significant number of patients on NSAIDs will develop serious complications involving the gastrointestinal tract [3, 4]. Assessment of these side-effects is important, not least in the development of the newer class of agents in this arena, the COX-2 selective inhibitors or *coxibs* [5–7]. Indeed, the platform for the clinical and commercial success of these latter agents has been built on the premise that they are far less injurious to the gut. Newer agents to challenge

Correspondence: Professor B. J. R. Whittle, William Harvey Research Institute, Barts & The London, Queen Mary's School of Medicine, Charterhouse Square, London EC1M 6BQ, UK. E-mail: b.j.whittle@qmul.ac.uk

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the supremacy of these claims include the nitric oxide (NO)-donating NO-NSAIDs, also known as CINODs (cyclo-oxygenase inhibiting nitric oxide donating agents), and the dual cyclo-oxygenase-lipoxygenase inhibitors, all of which are undergoing ever-rigorous evaluation for effects on both the stomach and small intestine. This whole area of the clinical evaluation of NSAID-induced gut injury has been dealt with in some depth by two of the reviews in this series and also in the paper on histopathological aspects of drug side-effects.

In the review article by James and Hawkey in this current issue (pp. 146–155), the authors provide an analysis of the quantitative techniques that can be employed by clinical pharmacologists and others to evaluate NSAID-induced damage in the upper gastrointestinal tract, particularly the stomach. These methods include the use of radio-labelled erythrocytes, gastric washing and endoscopy. The authors also provide an assessment of the data from a number of the clinical studies, with emphasis on the on-going debate on the actions of the *coxibs*, pointing out some of the pitfalls in protocol design.

The review by Smale and Bjarnason on determining small bowel integrity explores the use of a range of techniques available for Phase I clinical studies and beyond, including radio-isotopes such as ¹¹¹Indium used to label white cells to monitor their flux, or ⁵¹Chromium-EDTA or sugars used for detecting changes in small intestinal permeability. The determination of the novel technique to determine faecal calprotectin, a neutrophil-derived protein, is also discussed. The use of these techniques in the assessment of NSAID-induced dysfunction is described in some detail. The authors also point to the use of enteroscopy or capsule enteroscopy, which is likely to become more widespread in the clinical evaluation of new therapeutic agents.

Diseases of the large bowel provide targets of major unmet clinical need for pharmacological development and are the focus of much activity within the pharmaceutical industry. The diversity of the approaches and the range of new therapies for colonic dysfunction currently under consideration, require that clinical pharmacologists and gastroenterologists develop appropriate techniques for evaluation and definition of end-points.

Thus, Carty and Rampton, in their paper on new therapies for inflammatory bowel diseases (IBD), describe the problems associated with disease heterogeneity and other confounding factors in the design of clinical trials in IBD. These include stratification and choice of comparator, as well as the use of end-points of clinical activity indices, laboratory measures of inflammation and quality-of-life scores. They also review the range of methods available for evaluating the mechanism of actions of potential new drugs for IBD in the clinical setting. Studies on the gut lumen are described, such as whole-gut

lavage, colonic perfusion, rectal dialysis and the recent simple filter paper technique, accompanied by a review of the methods for evaluation of the mucosa and blood. Such techniques may well become an established part of the clinical pharmacologist's portfolio in this area.

Irritable bowel syndrome (IBS) has also attracted significant interest from the industry, and the range of newer pharmacological approaches that have been under development is appraised by Talley in his review. This is a multifaceted disease, which, due to the complexity and range of components and potential mediators involved, makes the development of fully operational experimental models difficult. As with the preclinical work, the clinical pharmacological studies for novel therapeutic agents or appropriate probes for testing hypotheses, have concentrated predominantly on the presenting symptoms of altered bowel habit and the perception of visceral pain. Distension of the gastrointestinal tract is well known to elicit visceral pain in human studies. Indeed, rectal distension by a luminal balloon has been employed in clinical pharmacology and in Phase II development studies with several novel therapeutic entities, as a surrogate index of potential efficacy in IBS.

The final aspect of this series is the role of gastrointestinal biopsy evaluation in drug development and is covered by two linked papers. Biopsies can be taken to make a diagnosis, assess progression or remission of disease and to help ascertain why, despite therapy, symptoms persist. Biopsies can also be used to assess side-effects of drugs, in conjunction with other tests of gut function. Although specialist pathologists conduct such procedures, the techniques should be considered by clinical pharmacologists when preparing their drug evaluation protocols, especially at later stages in the development schedule.

In the first of these papers, Walker considers the role of gastrointestinal biopsies in assessing a therapeutic response using sound, evaluated systems, covering the when, where, how and why to biopsy in drug development before you market the drug. The second review by Price focuses on a selected group of gastrointestinal diseases caused by drugs that are recognisable by the pathologist on evaluation of biopsies; thus, this covers how to assess drug damage to the gut using biopsies after you've put the drug on the market. Biopsy assessment is costly and their use should be carefully considered before undertaking this invasive procedure, but as these reviews demonstrate, can provide important information.

We have endeavoured in this series to cover as many disparate aspects of the current research methods relating to the gut as would be of interest to the clinical pharmacologists. It is clear that the use of appropriate and fully validated methodology will be crucial for the clinical development of newer drugs in this area. Such techniques to monitor gut function are also essential to gain

a clearer understanding of the absorption and bio-availability of drugs given via the oral route. The side-effect profile on the gastro-intestinal tract of a range of new chemical entities for different therapeutic utilities is gaining prominence, not least in the area of novel anti-inflammatory agents and COX-2 inhibitors. Thus, we would hope that this current review series of research methods in gastroenterology will be of practical use to clinical pharmacologists working in this area.

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