*Digestive Diseases and Sciences, Vol. 40, No. 2 (February 1995 Supplement), pp. 1S–2S*

# Introduction

## A Review of the Status of Omeprazole: The Hanbury Workshop

The consequences of acid suppression have provoked concern since the advent of effective pharmacological acid suppression by the $H_2$-receptor antagonists in the mid-1970s. The increased risk of gastric cancer following acid lowering surgical procedures and the Correa (nitrosamine) hypothesis have provided some support for these concerns. With the introduction of the proton pump inhibitor, omeprazole, this concern was raised again.

Regulatory approval of all acid-suppressing drugs is preceded by several methods of assessing safety, including tests for carcinogenicity, a survey of organs in two animal species following long-term administration of doses several times that used in humans, and careful clinical surveillance during clinical trials. By this means, side-effects (i.e., effects resulting from a primary mechanism of the drug) are usually well defined early in development. Furthermore, there is a worldwide reporting system which allows elucidation of rare or idiosyncratic events associated with the use of the drug which might not be obvious in early studies. These adverse events also have to be evaluated carefully to determine whether they are indeed drug related or part of the underlying disease. In the case of omeprazole, more than 90 million treatments have been prescribed worldwide. The drug has been shown to be safe and well tolerated in both short-term and long-term clinical use.

A careful and critical review of the relevant literature by ourselves indicated no scientific evidence in support of the concerns over the risks of therapeutic acid suppression. A search for independent or multisponsor support for a meeting to explore this important topic was, perhaps not surprisingly, unfruitful.

We therefore planned a novel approach to reviewing in depth the relationship between acid suppression and the possible risks that might ensue in as independent a manner as was possible with a single sponsor who had an interest in the area, namely Astra Hässle AB, Mölndal, Sweden.

The principle areas of interest were identified as topics for seven individual workshops. These were:

I. The mechanisms of acid secretion and potential therapeutic targets.

II. Appropriate acid suppression for symptom relief and healing in acid-related disorders.

III. The role of gastrin in acid secretion and its response to acid-lowering therapy.

IV. Hypochlorhydria, bacterial overgrowth, nitrosamines, and the potential for neoplasia.

V. The morphology of the gastric mucosa.

VI. Human models of hypo- and achlorhydria.

VII. Adverse events with acid-lowering treatments.

These topics were searched using MEDLINE and by recursive searching of review articles. All the references retrieved were carefully reviewed.

Eighty leading experts in the fields covered by the above workshops, who were also considered to be at the forefront as opinion leaders from around the world, were identified, invited as participants and allocated to the relevant workshop for their maximum participation.

The key 100 papers for each of the seven workshop topics were sent to each of the participants for the individual workshops, together with the full list of other references. Each participant was asked to identify whether the list was comprehensive and complete and to send details of any missing references and to identify whether the priority was appropriate or required alteration.

Each participant was then asked to make a list of ten key statements which they considered should be debated at the workshop. These were then circulated to each member of the relevant workshop and the participants were then asked to refine the statements and to prioritize all the submitted statements for



0163-2116/95/0200-001S$07.50/0 

discussion into "must cover," "try to cover," or "could omit if time not available."

At the meeting, there was an introductory plenary session to outline the key issues, the objectives, and to ensure that there was full comprehension as to the conduct of the meeting. The meeting then divided into the independent workshops. The priority and secondary statements were debated under the guidance of the workshop chairman and the results recorded by a rapporteur. Each lunchtime and evening all the delegates had access to a poster session at which all statements for each workshop were displayed. Participants were encouraged to add further relevant statements and comments to the existing statements for the workshops in which they were not participating, thus ensuring maximum peer review and input.

On the second day, the members of the seven workshops combined into two workshops to discuss specific issues better dealt with in a larger interactive and multidisciplinary environment, and ensure maximal cross-fertilization of knowledge and ideas. The meeting then returned to the seven independent workshops to conclude the specific objectives of each group. The meeting ended on the third day with a full plenary session at which each workshop presented their conclusions.

We believe that this comprehensive analysis permitted the most intensive, in-depth, and thorough review of this topic so far undertaken. The selection of material for consideration and the debates and conclusions were completely independent of the sponsor.

Such an approach seems to us as to be as objective a means as is possible for evaluation of the status of a drug, with respect to mechanism, efficacy, and safety. This publication is the result of this process.

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