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Abstract.Cimetidine and the treatment of duodenal ulcer.

This thesis examines the clinical development of the H₂-receptor antagonist cimetidine as a treatment for duodenal ulcer disease.

The work was carried out at the Royal Adelaide Hospital between 1976 and 1980, and partly in collaboration with Prince Henry's Hospital, Melbourne.

In Chapters one and two the historical evolution, aetiology and pathogenesis of duodenal ulcer disease are reviewed. The importance of acid-pepsin secretion by the stomach is emphasized. Chapter 3 describes the development and pharmacology of the histamine H₂-receptor antagonists, with particular emphasis on cimetidine.

A clear picture of the course and prognosis of duodenal ulcer is essential to allow logical design of treatment trials and to provide a yardstick against which the results of a new treatment can be judged. Chapter four provides a critical review of published studies on the natural history of duodenal ulcer and indicates the problems of interpreting existing data. The choice of different ways of expressing the course and outcome of this chronic, relapsing (but rarely fatal) disease is identified as an important factor contributing to controversy over the prognosis of duodenal ulcer.

In Chapter five the design of clinical trials in general and the particular methods that were chosen for the Adelaide studies are discussed. The importance of ethical safeguards, control groups, random allocation and choice of clear criteria

of response is emphasized.

The results of treatment of 85 duodenal ulcer patients with cimetidine for six weeks are presented in chapter six. Eighty four percent of cimetidine treated patients and thirty eight per cent of patients receiving placebo had healed ulcers, judged by endoscopy. Assessment of pain and antacid use confirmed the advantage of cimetidine over placebo in producing rapid relief of symptoms.

Longer term trials of cimetidine treatment were then undertaken. Following initial ulcer healing with a short course of cimetidine fifty six patients were randomly allocated to treatment with cimetidine or placebo for one year. The results demonstrated that ulcer relapse which occurred in most patients receiving placebo could be prevented in the majority of patients by cimetidine. (Chapter seven).

To try and assess whether prolonged cimetidine treatment conferred any lasting benefit, treatment was changed to placebo at the end of one year in a further double blind study (chapter eight). Ulcers recurred at a similar rate to that found in patients who had received only six weeks cimetidine to heal their ulcer. It was concluded that prolonged cimetidine treatment was unlikely to alter the natural history of duodenal ulcer disease, once the drug was stopped.

This observation raised the question of how cimetidine should best be used for the longer term management of duodenal ulcer. In order to attempt to answer this a further one year study was devised. Patients were randomly allocated to continuous maintenance treatment with cimetidine or intermittent

short courses of the drug for each recurrence (chapter nine).

Throughout all these studies no serious side effects attributable to cimetidine occurred. Small elevations in plasma creatinine were found (usually within the normal range) without significant impairment of renal function. One interesting observation was the interaction of cimetidine with warfarin and phenytoin (chapter ten). Further investigation supported the concept that cimetidine inhibits hepatic microsomal oxidation of drugs metabolised by this route.

The number of patients required to confirm the safety of the drug is much greater than the relatively small number of patients studied during these trials. Chapter ten therefore examines the safety and side effects of cimetidine by reviewing all available sources of information from clinical studies to spontaneous reports of adverse events. Minor unwanted effects are uncommon and serious side effects are extremely rare. In only a handful of the twenty million or more patients treated worldwide has cimetidine been thought to be a factor that may have contributed to their death. The safety of cimetidine as a life long treatment for peptic ulcer remains to be demonstrated.