Safety Profile of Ranitidine
A Review

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Summary

Ranitidine has been used for the treatment of millions of patients during the past 10 years. A small proportion of patients have developed a reaction to the drug shortly after the start of treatment, usually as a result of 'individual idiosyncrasy'. Reactions during continuous, long-term treatment with ranitidine are uncommon, so that maintenance treatment of the chronic peptic diseases with ranitidine for more than 10 years has not been associated with significant iatrogenic disease.

1. Effects of Ranitidine Treatment on Complications Associated with Ulcer Recurrence

During recurrence of ulcer disease, any patient may suffer from a complication, such as haemorrhage or perforation, which is potentially lethal. The development of a complication cannot be accurately predicted, but complications become more likely, and more serious, with (a) longer du-
ration of ulcer disease; (b) greater patient age; (c) previous history of complication of the ulcer; and (d) consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) [Penston & Wormsley 1992a]. As a result of these complications and of the risks of the surgical treatment of the complications, 80% of patients with gastric or duodenal ulcers have a serious clinical course and 1 to 2% die from the disease.

In considering the safety of treatment with ranitidine, it is therefore necessary to assess the likelihood of complications that occur during long term therapy compared with the probability of the development of complications in patients who are not receiving treatment, or who have stopped treatment.

A number of reports are now available which show that significantly fewer patients experience complications during continuous treatment with ranitidine. For example, in a 3-year US study of patients who had presented with bleeding duodenal ulcer, 9% of those receiving long term (maintenance) treatment with ranitidine experienced rebleeding during ulcer recurrence compared with 36% of patients receiving placebo (Jensen et al. 1990). In a French study of maintenance treatment with ranitidine for 2 years, ten times as many patients given placebo developed haemorrhage (5%) compared with patients receiving ranitidine (Ruszniewski et al. 1992). Similarly, in a Swiss/German multicentre study of continuous treatment with ranitidine for 2 years, haemorrhage occurred in 1.3% patient-years before, and 0.37% patient-years during, maintenance treatment (Blum et al. 1992).

In our study of continuous treatment with ranitidine for up to 10 years, the risk of haemorrhage decreased from 6.2 to 0.4% during the first year of maintenance therapy (Boyd et al. 1990) and in 10 years, less than 2% of patients with duodenal ulcer bled during ulcer recurrence, compared with 15% of patients who bled within 3 years while receiving no treatment (Penston & Wormsley 1992b). No perforation occurred during the study. Similarly, of 120 patients with gastric ulcer receiving continuous treatment with ranitidine for 7 years, no patient suffered from a complication, while 1 patient bled and 1 had a perforated ulcer when treatment was discontinued (Penston & Wormsley 1990).

It is clear, therefore, that long term treatment with ranitidine significantly decreases the likelihood that patients with gastric or duodenal ulcer will develop a complication while treatment continues.

2. Adverse Reactions to Ranitidine

2.1 General Incidence of Adverse Effects

A number of general reviews have shown that reactions to ranitidine during short courses or long term continuous treatment are uncommon.

In a study of reactions recorded in the Pennsylvania Medicaid Management Information System (MMIS) [Das et al. 1990], only diarrhoea and headache occurred in >1% of patients receiving treatment with ranitidine (table I). The values for the rates of diarrhoea, constipation and rash were approximately twice the control values, and that for headache was similar to control values. The study report emphasised that the recorded events represent associations and do not necessarily indicate causal relationships with the drug therapy.

Similarly, few adverse reactions were noted during the clinical trials summarised by Dawson et al. (1983). Most of the reactions did not require discontinuation of therapy.

Subsequent analyses reported that similar proportions of patients receiving ranitidine or placebo developed reactions, ranging from less than 1% up to 5% of individuals (Grant et al. 1989). No adverse effects were recorded during treatment of nearly 400 paediatric patients (De Angelis & Bandini 1989). In a 7-year drug surveillance study, the prevalence of adverse events was 0.87% in 22 080 ranitidine-treated patients, a value not significantly different from the problems recorded in placebo-treated individuals (Eandi et al. 1988).

It appears, therefore, that reactions to ranitidine in short term studies are uncommon and mostly occur soon after the start of treatment. The propor-