RANITIDINE AND GERD

TITLE: Clinical effectiveness and quality of life with ranitidine vs placebo in gastroesophageal reflux disease patients: a Clinical Effectiveness Network (CEN) study
AUTHORS: Rush DR, Stelmach WJ, Young TL, et al.
JOURNAL: *The Journal of Family Practice*
DATE: August 1995; Volume 41:126–136.

Clinical question. Compared with placebo, is ranitidine effective in patients with typical symptoms of gastroesophageal reflux disease (GERD)?

Background. Many controlled trials have demonstrated the efficacy of H_2 blockers in the treatment of GERD. Most of these studies have been in controlled research settings in which the diagnosis was confirmed by endoscopy. This large prospective study tested the effectiveness of ranitidine in family practice patients with a clinical diagnosis of GERD, without endoscopic confirmation of the diagnosis.

Population studied. Eight hundred twelve adult patients who had had clinical symptoms of GERD (defined as heartburn with or without other symptoms) for at least 3 months were identified by 143 family physicians during routine office visits. It is unclear whether all these patients had GERD, but it is possible that some had gastritis or peptic ulcer disease. Patients with other documented upper gastrointestinal problems, such as erosive esophagitis or ulcer disease, were excluded, as were patients with "symptoms of GERD refractory to prescription anti-reflux medications." The latter exclusion criterion has the effect of making the treatment look better than it is in an unselected group of patients. Of the 812 patients identified, full analysis was performed on a subgroup of 590 patients who were willing to follow the full research protocol (the "per-protocol" group). Since we are not told how many patients with symptoms compatible with GERD presented to the participating family physicians during the study period, we must assume some patient selection took place. Nonetheless, the investigators probably derived a fairly representative national sample of patients with mild to moderate heartburn. The representativeness of the sample is a major issue in this study, which claims to be "real-world."

Dr Hickner is from the Upper Peninsula Campus, Department of Family Practice, Michigan State University College of Human Medicine, Escanaba, Michigan. Address correspondence to John Hickner, MD, Suite 120, 2500 7th Ave S, Escanaba, MI 49829.

Dr Schwartz is from the Department of Family Medicine, Wayne State University, Detroit, and Grace Family Practice Center, Royal Oak, Michigan. Address correspondence to Kendra L. Schwartz, MD, MSPH, Grace Family Practice Center, 505 S Woodward, Royal Oak, MI 48067.

Study design and validity. This was a randomized, double-blind, placebo-controlled trial, the "gold standard" of drug efficacy studies. As one would expect from a study sponsored by a pharmaceutical company, the research methods appear to be very good. Randomization was determined by a computerized random number table, and the ranitidine and placebo tablets appeared identical. Patients were required to keep a diary during a 7- to 10-day observation period and during the 6-week study period. Only patients reporting a minimum of four 24-hour periods with at least one episode of heartburn during the observation period were eligible for the per-protocol group. Patients taking continuous medication for GERD during the 30 days prior to enrollment were excluded from this group. Laboratory assessment and diagnostic studies were not required but were permitted according to each clinician's judgment. Statistical analysis appears appropriate, though one would like to have seen the *P* value adjusted for multiple comparisons: the more comparisons made, the more likely that one will be significant by chance alone.

Outcomes measured. Outcomes measured included self-rated scores of the severity and frequency of symptoms, patient and physician global-assessment scores for reflux, and antacid use. The investigators also included two quality-of-life measurements: the well-validated SF-36 and a heartburn-specific quality-of-life questionnaire. Inclusion of quality-of-life measures in clinical trials is becoming more important in the current atmosphere of outcomes research and managed care.

Results. The randomization process apparently worked, since baseline data on the treatment and control groups were comparable. From a statistical viewpoint, ranitidine won hands down over placebo on all outcomes measured. From a clinical viewpoint, the superiority of ranitidine plus as-needed antacid over placebo plus as needed antacid was not nearly so impressive. On a five-point global assessment scale, patients rated ranitidine only 0.5 points better than placebo. On a six-point heartburn pain scale, ranitidine was only about 0.5 points better than placebo on multiple ratings throughout the 6-week treatment period. Five days into treatment, only 20% of the ranitidine patients reported sustained relief, and after 6 weeks, only 64% reported sustained relief. Even with the heartburn-specific quality-of-life scale, scores for the ranitidine group were generally only a few points better on a 100-point scale. Perhaps heartburn, when mild to moderate, is at most an irritation.

ISSN 0094-3509

Recommendations for clinical practice. The major strengths of this study are that patient selection and treatment are driven by clinical presentation rather than endoscopic diagnosis, and that the measured outcomes are patient-oriented. The study shows that patients presenting with heartburn have a small but probably clinically significant benefit from ranitidine. Given the small overall benefit and the high cost of ranitidine, comparison with antacids and lifestyle changes is also warranted.

John M. Hickner, MD
Escanaba, Michigan

RISK FACTORS FOR HIP FRACTURES

TITLE: Risk factors for hip fracture in white women
AUTHORS: Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, and Vogt TM for the Study of Osteoporotic Fractures Research Group
JOURNAL: *The New England Journal of Medicine*
DATE: March 23, 1995; Volume 332:767–73.

Clinical question. Which risk factors are associated with hip fractures in white women 65 years and older?

Background. The lifetime risk for hip fracture in white women is close to 20%. Risk factors for hip fracture have been identified in previous studies, including lower body weight, inactivity, and use of sedatives, caffeine, and tobacco. However, the studies that identified these risk factors were thought by the authors above to be flawed in design. According to them, the prospective study reported here is unusual in that many potential risk factors were included, as well as bone density measurements.

Population studied. The study population consisted of 9516 white women who were at least 65 years of age and had been recruited by mail in four different areas of the country between 1986 and 1988. Black women (because of their low incidence of hip fracture), women with a previous hip fracture, and women with bilateral hip replacement were excluded. During the study period, 192 participants had a hip fracture, 585 died, and 92 were lost to follow-up.

Study design and validity. Study participants were questioned and examined in an outpatient clinic. They were interviewed regarding medical history, medications, exercise, daily activity, and estimation of calcium and caffeine intake. Examination included anthropometry, neuromuscular function and strength, mini-mental status examination, visual and orthostatic testing, and calcaneal bone density measurement. Patients were contacted every 4 months for ascertainment of hip fracture (confirmed by review of the radiographs) and followed for an average of 4.1 years. We are not given the response rate of the women recruited for the study and, therefore, cannot judge whether this group is representative of all white women over age 65 or whether it suffers from significant selection bias. For example, women with more risk factors or a family history of osteoporosis might be more likely to volunteer for the study.

Outcomes measured. Risk factors for hip fracture were identified with regression analysis statistics. The estimate of risk used was relative risk (RR) with 95% confidence interval (CI). A risk factor with an RR of 1.0 or those with a CI that includes 1.0 are considered unlikely to be related to the outcome, which, in this case, is hip fracture. In addition, the authors were especially interested in whether some of the more significant risk factors were independent of the bone density measurements.

Results. Sixteen independent risk factors for hip fracture were identified. Those with an RR of 1.5 or greater included age, history of maternal hip fracture, self-rated poor health, previous hyperthyroidism, current use of long-acting benzodiazepines, current use of anticonvulsant drugs, on feet less than 4 hours per day, inability to rise from chair without using arms, poor depth perception, resting pulse rate greater than 80, and decreased calcaneal bone density. Factors that seemed protective (RR less than 1.0) included increase in weight since age 25 and walking for exercise. The incidence of hip fractures was directly related to the number of risk factors present. The hip fracture incidence rate among women with five or more risk factors and low bone density was 27 times greater than among women with fewer than three risk factors and normal bone density.

Some commonly believed risk factors, such as fair hair color, northern European ancestry, and earlier natural menopause, were not found to be significant. Although current smoking was not an independent risk factor, it still was associated with hip fracture. Estrogen therapy seemed to be protective in those women without a history of osteoporosis or fracture, but the CI was wide (RR=0.3; CI=0.1 to 1.1). Based on a single self-reported assessment during the study, calcium intake was not found to be related to hip fracture.