Omeprazole, H₂ blockers, and polyarthralgia: case-control study

Christoph R Meier, Hershel Jick

Acute polyarthralgia has been reported in five patients in association with the proton pump inhibitor omeprazole.¹ These patients did not have rheumatoid arthritis, concurrent infections, or connective tissue disorders, and their symptoms resolved after stopping omeprazole.¹ We compared the relative risk of developing acute idiopathic polyarthralgia during and after exposure to omeprazole, ranitidine, or cimetidine, antiulcer drugs used for similar indications.

Subjects, methods, and results

We conducted a nested case-control analysis using data from a UK general practitioner research database which provides the demographics, medical conditions, and drug prescriptions of over four million people.²⁻⁴

Cohort members comprised people aged 20-60 who had received at least one prescription for omeprazole, ranitidine, or cimetidine between 1 January 1992 and 31 December 1994 and had at least one year's medical history recorded on computer. Subjects were excluded if they had a history of idiopathic multiple arthralgia or had pre-existing rheumatic disease, gout, psoriasis, inflammatory bowel disease, chronic liver and renal disease, cancer, or diabetes mellitus. We followed up each cohort member for 360 days after they had been prescribed one of the drugs, identifying people who had idiopathic polyarthralgia for the first time leading to a referral to a specialist. We reviewed referral letters and laboratory test results of potentially eligible cases without knowing if they had been exposed to one of the drugs.

About 80 000 people were eligible for the cohort. There were about 90 000 prescriptions for omeprazole, 170 000 for ranitidine, and 120 000 for cimetidine. We identified 100 patients (mean age 46 years, 75 women) as having idiopathic polyarthralgia for the first time and 361 eligible controls (range 1-6 controls per case), matched for practice, age (within three years), sex, and date of diagnosis. Risk estimates in a matched analysis were obtained through conditional logistic regression in SAS.⁵

Patients who were currently taking omeprazole were not at higher risk than those currently taking ranitidine or cimetidine. Compared with ranitidine and cimetidine, the relative risk estimates for current and recent past use of omeprazole combined were 1.1 (95% confidence interval 0.2 to 5.6) and 0.8 (0.3 to 2.8), respectively, after adjustment for body mass index (<25, 25-30, and >30 kg/m²), smoking (current smoker, former smoker, non-smoker, and unknown), and whether the patient had previously taken one of the drugs studied. The risk of developing acute polyarthralgia from all three drugs was not substantially higher for current use compared with recent past use (drug last taken 1-90 days before the index date), past use (91-180 days before the index date), or distant past use (181-360 days before the index date) (table). The risk of idiopathic polyarthralgia was not

Adjusted relative risks of developing polyarthralgia after exposure to antiulcer drugs omeprazole, ranitidine, and cimetidine

Use	No of cases	No of controls	Relative risk (95% CI)
Omeprazole			
Current and recent past	12	43	0.8 (0.3 to 2.8)
Past	4	12	0.4 (0.1 to 4.7)
Ranitidine			
Current and recent past	30	87	2.1 (0.8 to 5.2)
Past	11	42	0.5 (0.1 to 6.2)
Cimetidine			
Current and recent past	15	60	1.0
Past	11	41	1.0
Omeprazole			
Distant past	17	76	1.0
Past	4	12	0.8 (0.1 to 8.3)
Recent past	4	15	0.3 (0.1 to 3.7)
Current	8	28	0.6 (0.1 to 4.9)
Ranitidine			
Distant past	17	76	1.0
Past	11	42	0.9 (0.3 to 2.9)
Recent past	14	33	1.1 (0.3 to 3.4)
Current	16	54	1.0 (0.4 to 2.8)
Cimetidine			
Distant past	17	76	1.0
Past	11	41	1.9 (0.6 to 6.4)
Recent past	6	26	1.2 (0.3 to 5.6)
Current	9	34	1.5 (0.3 to 6.5)

associated with duration of total exposure to the study drug before diagnosis, and dose dependence was not seen among current and recent past users of the three study drugs.

Comment

Our results suggest that omeprazole use is not associated with an increased risk of inducing polyarthralgia compared with ranitidine and cimetidine. The absence of increased risk of current drug use compared with use in the past or distant past makes a causal role for the study drugs unlikely. These findings, however, do not rule out the possibility that these drugs may sometimes cause adverse effects on the musculoskeletal system in particular people.

Funding: The Boston program is supported partly by grants from Astra Hässle, Bayer, Berlex Laboratories, Glaxo Wellcome, Hoechst, RW Johnson Pharmaceutical Research Institute, Novartis Pharmaceuticals, and Pfizer. CRM is supported in part by the Swiss National Science Foundation and the Ciba-Geigy Jubilaeums-Stiftung, Basel, Switzerland.

Conflict of interest: None.

- Beutler M, Hartmann K, Kuhn M, Gartmann J. Arthralgia and omeprazole. *BMJ* 1994;309:1620.
- Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;302:766-8.
- García Rodríguez LA, Jick H. Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs. *BMJ* 1994;308:503-6.
- García Rodríguez LA, Mannino S, Wallander M-A. Ocular safety of antiulcer drugs. *Lancet* 1995;345:1059-60.
- SAS Institute. *SAS/STAT Version 6.11*. Cary, NC: SAS Institute, 1995. (Accepted 21 May 1997)

Boston Collaborative Drug Surveillance Program, Boston University Medical Center, 11 Muzzey Street, Lexington, MA, 02173, USA

Christoph R Meier, research associate

Hershel Jick, associate professor of medicine

Correspondence to: Dr Meier chrmeier@bu.edu

BMJ 1997;315:1283