A cohort study of the ocular safety of anti-ulcer drugs

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- 1 Recently, some cases have been reported where intravenous use of omeprazole was followed by loss of vision. We followed up a cohort of close to 140 000 persons during periods of treatment and non-treatment with five anti-ulcer drugs.
- 2 The relative risk of vascular disorders of the eye during use of omeprazole compared with non-use was 1.8 (95% CI 0.5–6.0). Use of other anti-ulcer drugs was associated with a similar risk of vascular disorders. The relative risk associated with current use of any anti-ulcer drug was 1.9 (95% CI 1.1–3.4). We did not find a single case of optic inflammatory disorder during treatment with any of the five anti-ulcer drugs.
- 3 These results do not suggest a major increased risk for vascular or inflammatory disorders of the eye associated with use of omeprazole or other anti-ulcer drugs.

Keywords omeprazole anti-ulcer drugs ocular safety

Introduction

There is extensive literature on the ocular toxicity associated with numerous drugs [1]. All ocular structures can be affected, and the degree of visual impairment can vary from mild and reversible manifestations to permanent damage and blindness in the most serious instances^[2]. Also, changes or loss of vision may occur as an expression of neurotoxicity involving either the optic nerve, or the occipital cortex.

Serious disorders of vision had not been reported in association with omeprazole until 1993, when two cases of blindness were reported in Germany [3]. The patients experiencing these adverse events were severely ill and had been administered intravenous omeprazole together with a large number of other drugs in-hospital. In the months following the first report, more cases were notified to the company and regulatory authorities [4]. This spurred discussion about the scientific value and the regulatory implications of these case reports, which were unexpected in view of previous clinical experience with omeprazole and other anti-ulcer drugs. Possible mechanisms were hypothesized, and also an association of visual disorders with oral omeprazole was suspected [5–8].

Since no formal epidemiological data were available to provide estimates of risk, we conducted a retrospective cohort study on the association of oral treatment with anti-ulcer drugs and the risk of serious vascular and inflammatory disorders of the eye using the General Practitioners Research Database (GPRD) in the UK.

Methods

Data resource

Over 4 million residents in the UK are registered with general practitioners (GPs) who participate in the GPRD. These GPs use computers in their practices for the purpose of recording clinical information on their patients in a standard manner. Among other items, the recorded information includes prescriptions with indication for treatment, GPs notations, notes of hospital admission, specialist referral and laboratory tests. GPs have agreed to provide the information anonymously to the Office of Population Censuses and Surveys and to allow the information to be used in research projects.

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The completeness and validity of this database has been previously documented [9].

Study cohort

This study is an extension of a previous analysis which used a smaller study population and shorter study period [10]. The study population included all subjects aged 20–74 years, who received at least one prescription for cimetidine, famotidine, nizatidine, omeprazole or ranitidine between 1 January 1990 and 30 September 1994. Persons with a prior history of eye disorders, cerebrovascular disease, cancer, multiple sclerosis, brain disorders, hypertension or diabetes were excluded from the cohort.

Exposure definition

Person-time at risk contributed by a study subject started with the date of first prescription for an ulcer-healing drug, and ended with the earliest of the following: date of diagnosis of an eye disorder, date of development of one of the exclusion criteria, date of death or end of the study period. Three sequential time windows of exposure were defined for each anti-ulcer drug: 'current use' (from date of prescription until end of drug supply as written by the GP), 'past use' (90 days after the end of the 'current use' time window) and 'non-use' (all the remaining person-time after the end of the 'past use' time window). Person-time was further classified across strata defined by age, sex and calendar year.

Case ascertainment

We identified all subjects who had a first occurrence of an eye disorder recorded on the computer files. The following codes of the International Classification of Diseases 8th Revision were used; 341.0: CNS demyelination, 367.0: optic and retinal inflammation, 377.0: retinal vascular lesion, 377.1: degeneration of retina, 377.4: retinal disease, 377.5: papilledema, 377.6: optic nerve disease, 377.9: retinal and optic disease, 771.3:

blurred vision and 771.5: visual disturbance. The computerized patient profile of these subjects with personal identification suppressed was examined to exclude patients with pre-existing eye disorders, patients who were not referred to a consultant or a hospital, and patients with a presumed diagnosis recorded on computer which was not subsequently confirmed. Medical records were requested for the remaining patients from the GPs and were reviewed by a specialist in ophthalmology and at least one other author, without knowledge of drug exposure. After discussion, agreement among the reviewers was complete. Two groups of eye disorders were formed and evaluated: vascular and inflammatory disorders. A case of vascular eye disorder was defined as a person with a first occurrence of amaurosis fugax, occlusion or haemorrhage of the vascular system of the eye. A case of inflammatory eye disorder was defined as a person with a first occurrence of optic neuritis.

Analysis

Incidence rates for each anti-ulcer drug were standardized for age, sex and calendar year, using the distribution of person-time for the total study population as a standard. Estimates of the relative risk (RR) and their confidence intervals were calculated from the results of Poisson regression using the GLIM software. To be a confounder, a variable must be an independent risk factor for the disease. We tested for such association by comparing the prevalence of several gastrointestinal disorders which are the primary indications for ulcer-healing drugs, osteoarthritis, rheumatoid arthritis, collagen diseases and smoking in the case patients of vascular eye disorder with that in a random sample of 1 000 patients selected from the study cohort.

Results

A total of 140 128 persons contributed 345 803 person-years of follow-up experience. Subjects were followed for an average of 2.6 years. The age distribution of use

Table 1 Distribution of prescriptions by age for anti-ulcer drugs in study population

	Patients n	Prescriptions n	Age distribution of patients receiving prescriptions (years)		
			20–49 n (%)	50–64 n (%)	65–74 n (%)
Overall	140 128*	1 011 805	338 704 (33)	383 848 (38)	289 253 (29)
Cimetidine	68 504	342 382	115 145 (34)	131 627 (38)	95 610 (28)
Famotidine	3 141	19 055	6 795 (34)	7 558 (40)	4 702 (26)
Nizatidine	3 625	12 872	4 463 (35)	4 628 (36)	3 781 (29)
Omeprazole	33 988	146 933	52 282 (36)	53 728 (36)	40 923 (28)
Ranitidine	70 389	490 563	160 019 (33)	186 307 (38)	144 237 (29)

* Persons receiving at least one prescription for any of the five ulcer-healing drugs. 28% of the study subjects received more than one individual ulcer-healing drug during the period of study.

of individual anti-ulcer drugs is presented in Table 1. Anti-ulcer use was most common among men (54%). Medical records for 384 patients were requested from the GPs. We could not obtain medical records or the information was insufficient to assess the case status among 43 persons, therefore a total of 341 medical records were eventually reviewed. Table 2 shows the reasons for exclusion after review of medical records among 274 patients.

We identified 58 incident cases of vascular lesions of the eye. Forty-three cases were males and 12 cases were diagnosed in patients under the age of 60 years. The crude incidence rate was 11 per 100 000 person-years during non-use of anti-ulcer drugs. Occlusion of the retinal vein was the most frequent lesion, followed by retinal artery occlusion. Table 3 presents estimates of incidence rate and RR associated with individual anti-ulcer drugs. After adjustment for age, sex, and calendar year, the estimates of RR associated with current use were 1.8 (95% CI 0.5–6.0) for omeprazole, 2.1 (95% CI 1.1–4.1) for ranitidine and 1.9 (95% CI 0.9–4.1) for cimetidine compared with non-use. The RR associated with current use of any anti-ulcer drug was 1.9 (95% CI 1.1–3.4). Seven cases occurred during past use of

any anti-ulcer drug resulting in a RR of 0.7 (95% CI 0.3–1.7). Fourteen per cent of exposed cases developed vascular disorders of the eye during the first month of therapy, 43% between the second and sixth month and 43% after more than 6 months of treatment.

The risk was smaller among females compared with males (RR and 95% CI: 0.4, 0.2–0.6). Age was a strong predictor of the risk. The RR in persons older than 60 years of age compared with younger persons was 8.0 (95% CI 4.2–15.3). Twenty-one percent of cases presented with dyspepsia and 40% with peptic ulcer disease *vs* 35% and 39% respectively of 1 000 patients sampled from the study cohort. The prevalence of osteoarthritis, rheumatoid arthritis and collagen diseases was 26%, 4% and 0% among the cases and 20%, 2% and 0.5% among the random sample of 1 000 patients. Information on smoking status was available only on approximately 50% of cases and the random sample of 1 000 members of the study cohort. In this subset, smoking was not a risk factor for eye disorders.

Nine incident cases of optic neuritis were identified. The crude incidence rate was 3.7 per 100 000 person-years during non-use of anti-ulcer drugs. The median age at onset was 43 years (range 29–63 years). The proportion of women (67%) was similar to the one reported in a recent population-based epidemiologic study^[11]. Seven cases occurred during non-use, none during current use and two during past use of ranitidine.

Table 2 Patients excluded after review of medical records

Reason for exclusion	n	(%)
Macular degeneration	42	(15)
Other eye disorder*	56	(21)
Other exclusion criterion†	35	(13)
Diagnosis not confirmed in medical records	69	(25)
Prior history of eye disorder	72	(26)
Total	274	(100)

* There were 12 patients with cataract, 8 with disorders of vitreous, 8 with uveitis, 6 with glaucoma, 5 with trauma, 4 with muscle balance disorder, 4 with retinal detachment, 3 with congenital anomalies, 3 with retinal pigment changes, 2 with deficiency of tears and 1 with post-operative complication.

† There were 15 patients with cerebrovascular disease, 7 with hypertension, 6 with central nervous system disorders, 3 with computer entry errors, 2 with multiple sclerosis and 2 with cancer.

Discussion

These data show that the incidence of newly diagnosed vascular and inflammatory disorders of the eye, as defined in this study, is low in the general population. Current use of anti-ulcer drugs was associated with a small statistically increased relative risk of 1.9 (95% CI 1.1–3.4). There were more cases occurring among long-term users than at the beginning of anti-ulcer therapy, but no major differences between individual anti-ulcer drugs. The relative risk of vascular disorders of the eye during use of omeprazole compared with non-use was 1.8 (95% CI 0.5–6.0). With respect to the risk of

Table 3 Incidence rate and relative risk of vascular lesions of the eye during non-use, current and past use of ulcer-healing drugs (n = 58)

	Person-months	Number of cases	Incidence rate (per 10 000 p-years)	Relative risk* (95% confidence interval)
Non-use:	2280 234	21	1.1	1.0
Current use:				
Cimetidine	351 120	10	3.5	1.9 (0.9–4.1)
Famotidine	19 070	0	0.0	0.0 (0.0–18.3)
Nizatidine	11 714	0	0.0	0.0 (0.0–29.9)
Omeprazole	130 076	3	2.8	1.8 (0.5–6.0)
Ranitidine	516 852	17	4.0	2.1 (1.1–4.1)
Past use of any ulcer healing drug:	840 572	7	1.0	0.7 (0.3–1.7)

* The estimates of RR were adjusted for age, sex and calendar year.

inflammatory eye disorders, we could not find a single case during anti-ulcer treatment, and we could rule out with 95% confidence a risk greater than one per 10 000 individuals exposed to omeprazole.

We looked at whether certain other co-morbidities such as gastrointestinal disorders or other systemic diseases could be confounders. Our analyses indicated that major confounding was unlikely, however the prevalence of rheumatic disorders was twice as much among the cases than among the source population. Ocular involvement among patients with rheumatoid arthritis is common [12], suggesting minor overestimation of the risk associated with use of antiulcer drugs from residual confounding by this disorder. Confounding due to other risk factors such as smoking could only be partially evaluated in our population. Our study population was restricted to persons free of specific co-morbidity like cancer, hypertension and diabetes in order to control for confounding due to these risk factors. Accordingly, extrapolation of our results to populations with such co-morbidity should be tested with caution. It should also be noted that information on intravenous use of anti-ulcer drugs was not recorded on this general practice database. The finding of a greatly increased risk of vascular disorders of the eye with increasing age supports the validity of the data. The quality and completeness of the recorded clinical information in the GPRD database has been demonstrated in several studies and there is little reason to suspect that the results were due to bias in recording either exposure or outcome [13].

In summary, there is no indication that use of omeprazole or other oral anti-ulcer drugs is associated with a greatly increased risk for vascular or inflammatory disorders of the eye in our study population.

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