PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 7: 233–241 (1998)

ORIGINAL REPORT

Ocular Disorders in Users of H_2 Antagonists and of Omeprazole

SALVATORE MANNINO MD, MSc*,[1] MARIA GRAZIA TRONCON PhD[2], MARI-ANN WALLANDER PhD[3,4]
CHIARA CATTARUZZI PhD[2], FERDINANDO ROMANO MD, MSc[5], LUISA AGOSTINIS BSc[6],
PAOLA ERIKA MARIGHI MD[7] AND ALEXANDER WALKER MD, DrPH[8]
[1]*National Research Council, Institute of Advanced Biomedical Technologies, Milano, Italy*
[2]*Regional Directorate of Health, Regione Friuli Venezia Giulia, Trieste, Italy*
[3]*Department of Epidemiology, Astra Hässle AB, Mölndal, Sweden*
[4]*Department of Family Medicine, Uppsala University, Sweden*
[5]*Department of Biomedical Sciences, Faculty of Medicine, University 'G. D'Annunzio', Chieti, Italy*
[6]*INSIEL Spa, Udine, Italy*
[7]*Ophthalmology Department, St. Paul Hospital, University of Milan*
[8]*Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA*

SUMMARY

We have conducted a cohort study of users of omeprazole and H_2 antagonists in Italy to investigate whether the peroral use of these drugs may be associated with an increased incidence of ocular disorders leading to loss of vision. We have used the Sistema Informativo Sanitario Regionale (SISR database) in Friuli-Venezia-Giulia to identify all subjects who received at least one prescription for cimetidine, famotidine, niperotidine, nizatidine, omeprazole, ranitidine or roxatidine between 1 January 1991 and 31 December 1994. We have identified all hospital admissions for serious vascular or inflammatory ocular disorders following any such prescription, reviewed and validated all medical records. There were 71,108 users of any of the study drugs, contributing a total of 101,827 person years of observation. Seven cases of serious eye disorders were identified, giving an annual incidence rate of 7/100,000 persons. By comparison to non-users, the incidence rate ratio for current users of all of the study drugs together was 0, with a 95% confidence interval of 0 to 2.1. By comparison to non-users, the incidence rate ratio for past users was 0.47 (95% CI: 0.06–2.4). Our data are consistent with previous studies and add weight to the general impression of the ocular safety of these drugs. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — omeprazole; H_2 antagonists; drug safety; adverse effects; eye disorders

INTRODUCTION

Omeprazole is a proton pump inhibitor used in the treatment of benign gastric and duodenal ulcers, reflux esophagitis and Zollinger–Ellison syndrome. Omeprazole is prescribed in oral form at daily doses of 20–40 mg, and up to 120 mg in Zollinger–Ellison patients. In rare instances (mainly in seriously ill patients) and in some countries, it is also administered intravenously.

Following two anecdotal case reports coming from Germany, a question was raised in 1994 concerning whether the use of omeprazole i.v. may be associated with an increased incidence of ocular disorders leading to loss of vision.[1,2] Although the events of interest in the German reports had occurred in association with intravenous omeprazole, the question was extended to the oral form as well.[3–6]

A study already completed among outpatients using oral omeprazole and H_2 antagonists in

* Correspondence to: S. Mannino, National Research Council, Institute of Advanced Biomedical Technologies, Via Fratelli Cervi, 93-20090 Segrate, Milano, Italy.

CCC 1053–8569/98/040233–09$17.50

Accepted 23 December 1997

the United Kingdom has indicated no increase in risk associated with omeprazole.[7,8] Wishing to extend the range of relevant observations, we have undertaken a large cohort study of users of omeprazole and H_2 antagonists in Italy. We have taken advantage of the highly organized medical administrative data in the Region of Friuli-Venezia-Guilia to identify cohorts of drug users, and to link them to hospital admissions, and we have reviewed the medical records of persons admitted for possible ocular disorders.

MATERIALS AND METHODS

Source population and data

All Italian residents are registered with the National Health System, which provides medical services (including hospitalizations) offered by all public and many private providers, as well as all drugs included in the national drug formulary, partially or totally free of charge. Friuli-Venezia-Giulia (FVG) is a region of 1.2 million residents in the north-eastern part of Italy, bordering Slovenia and Austria and facing the Adriatic Sea. Since 1976 the Regional Directorate of Health in FVG has developed the Sistema Informativo Sanitario Regionale (SISR), a large automated regional database which collects data concerning all hospitalizations and prescriptions filled in the region, in addition to demographic information and a variety of specialized medical and administrative files.

The data sources used for the present research included the patient identification file, the hospital record file and the outpatient prescription file.

The patient identification file contains demographic information on all residents, and is updated daily. Data collected include: name, sex, date of birth, date of death, profession, address, changes in residence status and in the enrolment with a general practitioner, and designation of status entitling the citizen to special rights under the Italian social security system (e.g. diabetes, neoplasia, or epilepsy).

The hospital record file has collected information about all admissions to public and private hospitals within the region since 1985. Recorded data include age, sex, address, profession, admission and discharge diagnoses (up to four discharge diagnoses, recorded in ICD-9), diagnosis-related group (DRG), and vital status on discharge.

The outpatient prescription file contains information about the dispensing of drugs included in the National Drug Formulary, through public and private pharmacies. Data have been collected since 1991 or 1992, depending on the province within FVG. Information recorded in this file includes drug name and strength, the date the drug was dispensed, number of refills, patient's and physician's identification code. Beginning on 1 January 1994, reimbursement for H_2 blockers and proton pump inhibitors was limited to a maximum of 8 weeks of therapy for the following restricted list of indications: peptic ulcer, Zollinger–Ellison syndrome, hypersecretive gastritis, and gastro-oesophageal reflux disease. Reimbursement was denied for symptomatic treatment of pyrosis and in the prevention of GI diseases induced by aspirin, NSAIDs, or corticosteroids. Patients could still obtain them, but only by paying for the full drug cost out of their own pocket. Only reimbursed prescriptions are included in the outpatient prescription file.

Study cohort definition

All subjects who received at least one prescription for cimetidine, famotidine, niperotidine, nizatidine, omeprazole, ranitidine or roxatidine between 1 January 1991 and 31 December 1994 were identified. From this group we removed those who had prior hospital admissions with any of the anticipated disease endpoints listed in Table 1, and those with any diagnosis, procedure, or special status flag indicating prior substantial ocular disease, or disease that would interfere with evaluation of visual function. These are listed in Table 2. The remaining study population was by these selections intended to be free of previous episodes of visual loss, as well as glaucoma, cataract, cerebrovascular disease, cancer, multiple sclerosis, CNS disorders, and diabetes. Hypertensive patients were excluded if they had been hospitalized with a primary diagnosis of hypertension prior to their first prescription of an anti-ulcer drug.

The study population was followed from the time of first dispensing of an anti-ulcer drug during the study period until the earliest of the following terminating events: hospitalization for an endpoint listed in Table 1; hospitalization for one of the exclusionary conditions or with one of the exclusionary procedures or dispensing of one of the exclusionary drugs listed in Table 2; 365 days following the last prescription for an anti-ulcer drug; death; transfer of residence status from FVG to another region; the end of 1994.

Table 1 — List of study outcomes

ICD 9 code	ICD 9 description
362.18	Retinal vasculitis
362.3	Retinal vascular occlusion
362.55	Toxic maculopathy
362.81	Retinal haemorrhage
362.84	Retinal ischaemia
363.0	Focal chorioretinitis and focal retinochorioiditis
363.1	Disseminated chlorioretinitis and disseminated retinochorioiditis
363.2	Other and unspecified forms of chlorioretinitis and retinochorioiditis
363.61	Choroidal haemorrhage, unspecified
364.0	Acute and subacute iridocyclitis (*excludes 364.03, infectious*)
364.4	Vascular disorders of iris and ciliary body
368.11	Sudden visual loss
368.12	Transient visual loss
368.4	Visual field defects
369	Blindness and low vision
377.00	Papilledema, unspecified
377.03	Papilledema associated with retinal disorder
377.1	Optic atrophy, unspecified
377.12	Postinflammatory optic atrophy
377.15	Partial optic atrophy
377.3	Optic neuritis (*excludes 377.33 'nutritional . . .*')
377.4	Other disorders of optic nerve
377.53	Disorders of optic chiasm associated with vascular disorders
377.54	Disorders of optic chiasm associated with inflammatory disorders
377.62	Disorders of other visual pathways associated with vascular disorders
377.63	Disorders of other visual pathways associated with inflammatory disorders
377.72	Disorders of visual cortex associated with vascular disorders
377.73	Disorders of visual cortex associated with inflammatory disorders
377.9	Unspecified disorder of optic nerve and visual pathway
379.23	Vitreous haemorrhage

Each day of observation of each of the cohort members was classified by age and calender year of follow-up. In addition, each day was classified according to drug use. 'Current use of drug D' was defined as the estimated duration of a given prescription for drug D; current use started the day following the date drug D was dispensed and ended on the last day of treatment for that prescription. The duration of a given prescription was calculated by dividing the total amount dispensed by the defined daily dose (DDD). DDD was taken from WHO definitions,[9] augmented on an *ad hoc* basis for niperotidine, not covered by the WHO and for which a DDD of 230 mg was chosen. 'Past use of drug D' started the first day after the end of current use and lasted 90 days. 'Non-use' started the first day after the end of past use and lasted until the end of follow-up. For 'current' and 'past' use we aggregated all person-time in drug specific categories. Non-use person-time was aggregated into a single category, without distinguishing between drugs, to be used as the reference for all comparative analyses of the incidence of endpoints. For each of these exposure definitions, a new dispensing of a study drug caused the termination of the then-existing exposure category, and the initiation of a new sequence of exposure categories for the new drug, using the same definitions.

Case definition and ascertainment

Cases were individuals who had a hospitalization for new, acute visual loss resulting from vascular or inflammatory lesion of the eye. To identify these individuals, we searched the computerized files for all cohort members with a first time recorded hospital discharge diagnosis corresponding to any of the endpoint codes listed in Table 1 during the study period. We reviewed and abstracted the

Table 2 — List of exclusion criteria

ICD 9 code	ICD 9 description
2.1 ICD 9 Diagnoses	
140–208	Malignant neoplasm
224	Benign neoplasm of the eye
225	Benign neoplasm of the brain and other parts of nervous system
228.03	Hemangioma of retina
234.0	Carcinoma *in situ* of eye
250	Diabetes mellitus
290–294	Organic psychotic conditions
303, 305.0, 535.3, 571.0, 571.3	Alcohol related condition
320–326	Inflammatory disease of the central nervous system
340	Multiple sclerosis
341	Other demyelinating diseases of central nervous system
348	Other conditions of brain
364	Disorders of iris and ciliary body (*excludes 364.4*)
365	Glaucoma
366	Cataract
370–371	Keratitis, corneal opacity and other disorders of cornea
376	Disorders of the orbit
378	Strabismus and other disorders of binocular eye movements
379	Other disorders of the eye (*excludes 379.2*)
415	Pulmonary embolism
427.3	Atrial fibrillation
430–438	Cerebrovascular disease
800–804	Fracture of skull
850–854	Intracranial injury, excluding those with skull fracture
870–871	Open wound of ocular adnexa and eyeball
900	Injury to blood vessels of head and neck
921	Contusion of eye and adnexa
950	Injury to optic nerve and pathways
2.2 ICD 9 Procedures	
01	Incision and excision of skull, brain and cerebral meninges
02	Other operations on skull, brain and cerebral meninges
08–16	Operations on the eye
35	Operations on valves and septa of heart
36	Operations of vessels of heart
37	Other operations on heart and pericardium
38	Incision, excision, and occlusion of vessels
39	Other operations on vessels
97.31	Removal of eye prosthesis
2.3 ATC drug codes	
ATC code	ATC description
A 10	Antidiabetic therapy
B 01	Antithrombotic agents
L 01	Cytostatics
L 02B	Hormone antagonists and related agents
L 03	Immunostimulating agents
N 07X	Other CNS drugs (includes ganglioides)
S 01E	Antiglaucoma preparations and miotics

hospital records for all such people to confirm the recorded diagnosis, and to identify and exclude all patients who had one of the exclusionary conditions listed in Table 2, or who presented with the signs of a hypertensive retinopathy. From the hospital record we identified the date of onset of symptoms leading to the hospitalization. Each case was classified into an exposure category that corresponded to his or her exposure status on the day that symptoms began. Both reviewers and chart abstractors were blinded to drug exposure status of the potential cases.

Analysis

Person days in each category of drug exposure, age, and calendar year were summed and divided by 365 to obtain the number of person years of exposure. Crude incidence rates were calculated by further summation of exposure time over age and year into exposure categories for each drug, and dividing these numbers of months into the counts of cases in each category. Relative incidence rates were obtained by dividing the crude incidence rate in each exposure category by the crude incidence rate in category of non-use. Exact 95% confidence intervals (95% CI) with the mid-*P* correction were calculated using the adaptation of Fisher's exact test to confidence interval estimation as proposed by Martin[10] and implemented by Martin in the program Exact.[11] Repeat analyses carried out with stratification by age yielded results essentially identical to the crude results, and are not presented here. Mid-*P* values are two-sided and are derived from Fisher's exact test, adapted for person time data.

RESULTS

Study population

There were 71,108 users of one of the study drugs. There were 101,827 person years of observation in the cohort, giving an average follow-up of 1.43 years. The number of person years of follow-up that occurred in current users of one of the study drugs was 17,649, 38,664 person years were classified as past use, and the remaining 45,514 were non-use. Overall, 18.4% of person years were recorded by persons aged 20–39 years; 47.4% was in persons aged 40–59 years; 35.7% was in persons 60–74 years of age. The age distribution of study subjects was similar among the different drugs and across the different time periods examined.

Case ascertainment

There were 78 hospitalizations that met the screening criterion of the first time occurrence of one of the diagnostic codes listed in Table 1. We were able to obtain all the corresponding charts for review. Cases that were eliminated after review are summarized in Table 3.

In all there were seven cases of new, severe visual disorders requiring hospitalization. None occurred among current users of any of the study drugs, two were in past users (both following omeprazole), and five were in non-users (all former ranitidine users). There were no cases in the 20–39 years age group, four among 40–59-year-olds, and three in 60–74-year-olds.

Incidence of hospitalization for new visual loss

The details of person time and case occurrence by study drug are given in Table 4. The overall rate of hospitalization for new visual loss in this study was seven cases in 101,827 person years, giving an annual incidence rate of 7/100,000 persons.

By comparison to non-users, the incidence rate ratio for current users of all of the study drugs together, in whom no cases were reported was 0, with a 95% confidence interval of 0 to 2.1. By

Table 3 — Causes for exclusion of 71 identified cases after review of the medical records

Hypertensive retinopathy	18
Age-related macular degeneration	13
Myopic retinopathy	7
Central serous chorioretinopathy	4
Disorders of the retinal pigment epithelium	4
CNS disorder	3
Prior history	3
Glaucoma	2
Diabetic retinopathy	2
Alcoholic toxic optic neuritis	2
Other eye disorder*	7
Computer error	3
Insufficient information	2
Diagnosis not confirmed	1

*Includes cases of: neoplasm, post-traumatic retinopathy, hereditary degenerative retinopathy, dacryostenosis, paresis of abducent nerve, post-infectious eye disorder, posterior vitreous detachment.

Table 4 — Incidence of hospitalization for severe visual disturbance among users of gastroprotective agents Friuli-Venezia-Giulia, 1991–1994

	Current use			Past use		
	Cases	Person years	Rate ratio* (95% CI)	Cases	Person years	Rate ratio* (95% CI)
Ranitidine	0	10,123	0 (0–3.7)	0	24,326	0 (0–1.5)
Omeprazole	0	3096	0 (0–12.1)	2	5699	3.2 (0.43–16.2)
Cimetidine	0	1844	0 (0–20.3)	0	2972	0 (0–12.6)
Famotidine	0	1436	0 (0–26.0)	0	2944	0 (0–12.7)
Others/combinations	0	1149	0 (0–32.5)	0	2723	0 (0–13.7)
Non-use of any of the above	5	45,514	1.0			

*Versus non-use of any agent.

comparison to non-users, the incidence rate ratio for past users was 0.47 (95% CI: 0.06–2.4). As reported in Table 4, the incidence rate ratios comparing each of the drug exposure groups (current or past) to all non-users combined were compatible with either an absence of any effect of drugs on risk, or a large increase in risk.

Omeprazole was the second most commonly used of the study drugs, after ranitidine. No cases were observed among current omeprazole users, leading to a rate ratio of 0 (95% CI: 0–12.1) when compared to non-users of all drugs. Two cases were observed among past omeprazole users, resulting in a rate ratio of 3.2 (95% CI: 0.4–16.2) when compared to non-users of all drugs.

Case reports

Because of the small number of cases and the consequent sensitivity of the analysis to the classification of each case, we present the details of each of the seven numerator events below.

Case 1. A 67-year-old male was hospitalized because of a 5-day history of reduction in vision. Apart from the absence of diabetes, past history was unhelpful. He had received a prescription for ranitidine 8 months (251 days) previously and was taking no drugs at the time of onset of symptoms. On addition, blood pressure was normal. Corrected visual acuity was 10/10 OD and 3/10 OS. Funduscopic examination was unremarkable in the right eye. Examination of the left eye revealed macular haemorrhage. Neither fundus showed evidence of hypertensive retinal vascular disease. Fluorangiography showed arteriolar occlusion of the supratemporal branch of the retinal artery. The discharge diagnosis was retinal vascular occlusion of the left eye.

Case 2. A 62-year-old female who had experienced a sudden decrease in vision in the left eye 15 days earlier was admitted for papilledema. She was a treated hypertensive with hypertriglyceridemia, a history of gastropathy, and a smoker. She reported on admission that she was currently being treated for gastropathy with H_2 blockers, although in the prescription file her last record of a dispensed prescription for an H_2 blocker was a ranitidine prescription dispensed 4 months (116 days) earlier. On admission visual acuity was 10/10 in the right eye and 2/10 OS. She was treated in hospital with indapamide for hypertension and ranitidine, plus heparin and ergotamine. Vision in the left eye recovered to 9/10 by the fourth hospital day. Funduscopic examination of the right eye showed normal optic disc, vessels and macula. In the left eye there was disc swelling; vessels and macular were normal. Echo Doppler examination of the supra-aortic vessels showed an extended intimal thickening of distal third of the left carotid artery, with no evidence of stenosis. Ophthalmic, subclavian, and vertebral arteries were normal. Intraorbital and intracranial computerized axial tomographic examinations were negative. Discharge diagnosis was isolated oedematous optic

neuropathy in the left eye. The rapid drop and equally rapid recovery of vision suggests a combined diagnosis of papillitis and papilledema.

Case 3. A 43-year-old woman described a veil in the central part of her visual field, beginning 5 days before admission in September, 1993. In 1992 she had trigeminal neuralgia, and in April 1993 an evaluation for vertigo that included CAT scans and echo Doppler was negative. There was no personal or family history of hypertension or diabetes. Current medications included tenoxicam (an NSAID) dispensed a week prior to admission, plus a combination of bromazepam (a benzodiazepine), propantiline (an anticholinergic), dispensed a year earlier, but which she reported taking at admission. She had received ranitidine 6 months (199 days) previously. On admission, blood pressure was 160/110. Corrected visual acuity was 10/10 in both eyes. Funduscopic examination was normal in both eyes. Evoked visual potentials showed reduced amplitude and increase in latency in the right eye. The left eye was normal. Visual fields indicated an abnormal enlargement of the blind spot and a separate, relative cecocentral scotoma in the right eye. Neurologic examination was negative for focal signs. Discharge diagnosis was retrobulbar optic neuritis of the right eye.

Case 4. A 44-year-old woman with a past history of gastric ulcer and labyrithitis experienced pain and progressive blurring of vision in the right eye, beginning 15 days prior to admission. There were no current medications at admission. Ranitidine had been last dispensed, for the gastric ulcer, 5 months (174 days) prior to onset of symptoms. On admission visual acuity was 9/10 OD and 10/10 OS. Funduscopic examination in the right eye revealed indistinct margins of the optic disc, flame haemorrhage along the central retinal vein, tortuosity of the vessels, and retinal oedema at the posterior pole. The left eye examination was normal. Discharge diagnosis was retinal vein occlusion in the right eye.

Case 5. A 66-year-old male with an 8-year history of duodenal ulcer, treated periodically with H_2 blockers, reported spots in the visual field of his left eye for 10 days. He was taking no current medications at admission. The most recent anti-ulcer prescription was for ranitidine, dispensed 9 months (284 days) previously. Visual acuity was normal in both eyes, as was the funduscopic examination of the right eye. The left eye showed papilledema with marked swelling of the optic disc, venous swelling, peripapillar intraretinal flame haemorrhages, and intraretinal haemorrhage outside the posterior pole. A large soft exudate was present around the inferotemporal venous trunk. The arteriolar network was normal. In hospital, the patient experienced occasional extra-systolic atrial arrhythmias. Discharge diagnosis was partial occlusion of the central retinal vein of the left eye.

Case 6. A 56-year-old male with hypercholesterolemia and hypertriglyceridemia and a bleeding gastric ulcer 2 months earlier reported loss of vision in the upper portion of the visual field in his left eye 2 h before admission. He had recently obtained a single, 20-day supply of omeprazole, which had been dispensed 24 days earlier. Visual acuity was 10/10 OD; in the left eye there was light perception only. Funduscopic exam of the right eye showed vessels of slightly reduced calibre. In the left eye there was a reduction in colour of the anterior vessels, and a marked narrowing of the inferotemporal branch of the retinal artery. There was macular oedema with retinal pallor in the inferior segment. The optic disc was normal. Discharge diagnosis was occlusion of central retinal artery of the left eye.

Case 7. A 54-year-old woman with a history of surgery for duodenal ulcer felt acutely ill with confusion and vertigo, followed by sudden reduction of vision in the right eye 3 days prior to admission. She had been taking omeprazole for 6 months prior to the onset of symptoms, which came 29 days following the dispensing of the most recent 20-day supply. Corrected visual acuity was 6/10 OD and 10/10 OS. Funduscopic examination of the right eye revealed hyperemic optic disc with indistinct margins, venous congestion, and flame haemorrhage through the retina in the right eye. The fundus of the left eye was normal. Discharge diagnosis was occlusion of central retinal vein of the right eye.

It has to be reported that by extending the observation period of the cases after the end of follow-up, we found that case 3 1 year later had been diagnosed with multiple sclerosis. Although it is likely that the diagnosis of optic neuritis could be the first symptom of multiple sclerosis, we have decided to retain this subject in the analysis since — according to the study protocol — only the information collected within the follow-up

period could be used for the analysis. On the basis of this information, patient 3 was not classified as a multiple sclerosis patient and therefore did not meet this exclusion criterion.

DISCUSSION

Serious eye disorders of vascular or inflammatory origin proved to be extremely uncommon in the FVG region during the period of study, occurring in approximately seven per 100,000 patients per year. None occurred in 'current' users of any of the study drugs. Two cases occurred in 'past' omeprazole users. The results for the individual drugs are not statistically distinguishable from one another. The finding for omeprazole of a relative risk of 3.2 (95% CI 0.3–19.5) comparing past users of omeprazole with non-users of all drugs, is consistent with that observed among general practice patients in Britain. The incidence of acute visual loss in non-users of all drugs, here 5/45,514 or 11 per 100,000 per year, is identical to that seen in the British study.

The confidence intervals for the associations between visual loss of inflammatory or vascular origin and the use of ranitidine and of omeprazole largely overlap one another, and include an estimate of no risk attributable to either. Among users of both drugs, as in the general population, the incidence of these serious eye disorders is extremely low.

The interpretation of these findings should take into account potential limitations concerning the quality and completeness of the information collected for this study, although these are unlikely to challenge our conclusions.

Misclassification of exposure

Two potential sources of misclassification of exposure might have affected the results. First, the change in reimbursement practices for anti-ulcer drugs in 1994 implies that our classification of person time was in error for some persons in that year. Residents who continued to take H_2 blockers or omeprazole without reimbursement would have incorrectly contributed some 'current' use person time to the 'past' and 'non-use' categories. This error, if present, would only marginally affect the results. In fact such misclassification would apply to a small proportion of the entire volume of anti-ulcer drugs used by the study population.

Misclassification resulting from changes in reimbursement practices might explain the discrepancy between the medical records and the SISR with regard to drug exposure observed in case 2, who reported on admission that she was a current user of an H_2 blocker.

A second source of misclassification is related to the use of DDD (as recorded in the SISR) to define the duration of a prescription and therefore the length of the exposure category of 'current' use. The distinction between 'current' and 'past' users in this and similar studies is a matter of degree rather than a qualitative one. This is because anti-ulcer medications may not be taken exactly as prescribed, and there may be some medication left over at the end of the prescribed medication period, which we used to define current exposure. To the extent that this is true, 'past' and even 'non-use' exposure periods have to be viewed as intervals of progressively lower probabilities of drug consumption. Review of individual patient prescription histories indicates that the interval between refills of a regularly used medication is somewhat larger than the number of defined daily doses associated with the dispensed amount (data not shown).

Although this type of potential error is non-differential across all drug exposures, it might have more relevant implications for cases 6 and 7, both omeprazole 'past' users, who might conceivably have been taking omeprazole at the time of admission, even though this was not mentioned in the medical record. An analysis that incorporated this possibility would also have to merge the person time contribution from what we have called 'current' use and some substantial part of 'past' use.

Completeness of case ascertainment

The potential for underascertainment of cases in this study is limited. The present study was confined to patients admitted to hospital, whereas some cases of acute visual loss may have been handled on an outpatient basis. In FVG, however, most patients with recognized acute visual loss will be admitted to hospital, according to local ophthalmologists. Although we do not have reference epidemiologic data from Italy and the UK, the similarity of the overall incidence rate to that observed in the British study, which was based on outpatient records kept by general practitioners, strengthens the likelihood that most serious cases were identified.

Conclusion

Our data are consistent with previous studies and add weight to the general impression of the ocular safety of these drugs. These findings only apply to oral forms of the drugs. With respect to omeprazole, its risk profile is in line with that of other anti-ulcer drugs.

REFERENCES

1. Anonymous. Warnhinweise: Omeprazole (Antra) parenteral: Sehstörungen und blindheit. *Arznei-Telegramm* 1993; **7**: 74.
2. Anonymous. Netzwerk aktuell: Seh-und Hörstörungen nach Omeprazole (Antra, Gastroloc). *Arznei-Telegramm* 1993; **11**: 122.
3. Schönhöfer, P. S. Intravenous omeprazole and blindness. *Lancet* 1994; **343**: 665.
4. Creutzfeld, W. C. and Blum, A. L. Safety of omeprazole. *Lancet* 1994; **343**: 1098.
5. Colin-Jones, D. G. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343**: 1369.
6. Schönhöfer, P. S. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343**: 1370.
7. García-Rodrıguez, L. A., Mannino, S. and Wallander, M. A. Ocular safety of antiulcer drugs. *Lancet* 1995; **345**: 1059–1060.
8. García-Rodríguez, L. A., Mannino, S., Wallander, M. A. and Lindblom, B. A cohort study of the ocular safety of anti-ulcer drugs. *British Journal of Clinical Pharmacology* 1996; **42**: 213–216.
9. *Anatomical Therapeutic Chemical (ATC) Classification Index*. WHO *Collaborating Centre for Drug Statistics Methodology*. January 1994.
10. Martin, D. and Austin, H. An efficient program for computing conditional maximum likelihood estimates and exact confidence limits for a common odds ratio. *Epidemiology* 1991; **2**: 359–362.
11. Exact V 2.0 a. David D. Martin. Beth Israel Hospital. Boston, MA 02215, USA.

