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ORIGINAL REPORT

Omeprazole and Visual Disorders: Seeing Alternatives

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SUMMARY

In the WHO data base, visual disorders reported spontaneously with omeprazole, ranitidine and cimetidine, are very rare in the context of the widespread use of these drugs. There is a maximum reporting rate of severe visual impairment possibly ascribed to i.v. omeprazole of 0.94 reports per million treatment days in one year and in one country, Germany. This gives the worst quantitative case scenario for omeprazole by a single route of administration, to be compared with the worldwide reporting rate of all severe visual disorders by all routes of administration — 0.008 reports per million treatment days. Moreover, the reported visual abnormalities have a varied pathophysiological aetiology and their number increased in Germany after the first signal was raised in that country. Thus, apart from a direct causal relationship, solicited reporting artifact is one alternate plausible explanation for the apparent excess of cases of visual disturbance to omeprazole compared with cimetidine and ranitidine. That reporting rates of clinical events on newly marketed drugs are generally higher than with older drugs is a second factor for higher reporting rates with omeprazole. Vasculitis has been suggested as an aetiological factor, but the even lower reporting rate of this reaction makes this an unlikely hypothesis without any other supporting evidence. The authors are unaware of any drug that has caused a vasculitis solely affecting the eye.

Information on the prevalence of relevant visual disorders in the community would have been of considerable help in interpreting this signal, and a case control study of visual events in relationship to severe illness would be of public health interest, since no data seems to exist concerning this.

KEY WORDS — omeprazole; cimetidine; ranitidine; vision; adverse events

INTRODUCTION

A drug safety signal was raised in Germany[1,2] based on two individual case reports linking intravenous omeprazole with vision disorders including blindness. One of these cases and some further cases were diagnosed as resulting from anterior ischaemic optic neuropathy (AION) and resulted in wider publicity within Germany[3,4] and internationally.[5–7]

Not all the cases reported were consistent in apparent aetiology, however. In particular those related to later reports on oral, rather than intravenous, omeprazole use were often minor disorders or vaguely described as 'vision disorder' and 'blurred vision'. There was considerable media interest in Germany and elsewhere[8] and, in view of the widespread use of the drug and the clinical importance of such an ADR signal, it was necessary to determine, as rapidly as possible, the extent of the potential public health problem.

This paper represents a more complete analysis of data used during the early assessment of the problem, shortly after the signal attracted media attention.

MATERIALS AND METHODS

Using a common reporting format, spontaneously reported cases of suspected adverse reactions from 42 countries are stored in a data base maintained by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden. The data base contains at present well over 1.3

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Table 1 — Reporting rate of all vision disorders

Drug	Germany, UK and USA			All countries		
	No. of reports	No. mill. trt days	No. reports/ mill. trt days	No. of reports	No. mill. trt days	No. reports/ mill. trt days
Omeprazole	90	726.3	0.12	103	1657.0	0.06
Cimetidine	170	5396.8	0.03	199	9741.2	0.02
Ranitidine	210	7010.0	0.03	261	13,518.3	0.02

Table 2 — Reporting rate of blindness/severe vision disorders

Drug	Germany, UK and USA			All countries		
	No. of reports	No. mill. trt days	No. reports/ mill. trt days	No. of reports	No. mill. trt days	No. reports/ mill. trt days
Omeprazole	14	726.3	0.02	14	1657.0	0.008
Cimetidine	18	5396.8	0.003	21	9741.2	0.002
Ranitidine	20	7010.0	0.003	25	13,518.3	0.002

million individual case records, thus providing a valuable source of international ADR information. From this data base, adverse reaction reports on all vision disorders from 1983–1993 inclusive (for which sales data were available for all three drugs, see below) were incorporated in a search on omeprazole and on cimetidine and ranitidine as comparators. Reporting rates from Germany, UK and USA (target countries) were analysed in more detail since they constituted 90% of the total number of case records.

Corresponding drug utilization data were obtained from IMS International. This organization has been collecting data on drug use for many years in the major markets of the world, and its data base contains the only internationally comparable data relevant to the problem of providing a valid denominator, except for ex-manufacturer sales. The data collected by IMS are of two types: (i) census audits of drug sales; and (ii) continuing studies of disease and therapy.

From the IMS data base total sales in kilograms for omeprazole, ranitidine and cimetidine were broken down into oral and i.v., country and year. For comparability the sales figures were expressed as million treatment days per year. To obtain these figures, the total sales in kilograms from the IMS data base were divided by the Defined Daily Dose (DDD) value for each drug. The DDD for omeprazole is 20 mg, for cimetidine and ranitidine the DDDs are 800 mg and 300 mg, respectively.

Using the ADR and drug use data from the three countries which reported almost all the vision disorders gives the 'worst case scenario'. A 'best case' ratio was also made: all reports of vision disorders in the WHO data base to the three drugs divided by global drug use expressed in million treatment days (both parameters 1983–1993). The 'worst case scenario' is likely to have a bias towards an overestimate because of the choice of only those countries with most reports, though underreporting must be considered even for these countries in respect of true incidence. The 'best case scenario' should be an underestimate since not all countries in which the drugs are sold have ADR reporting systems, or have not reported vision disorders.

The annual overall reporting rates of all ADRs from the target countries were used as a background to the reporting of vision disorders.

RESULTS

For the purpose of this analysis, no attempt has been made to confirm the clinical details of the cases reported, and total validity in attribution has been assumed.

Blindness and clinically severe and acute visual disturbances were analysed separately from the total reports of vision disorders.

Over the period, the reporting rates of all vision disorders and blindness/severe vision disorders in association with the drugs are given in Tables 1 and 2, for the target countries, and for all countries. For severe vision disorders, the overall reporting rate for omeprazole, i.v. and oral together, appears to be about seven times that of the other drugs in the target countries, but four times greater on a

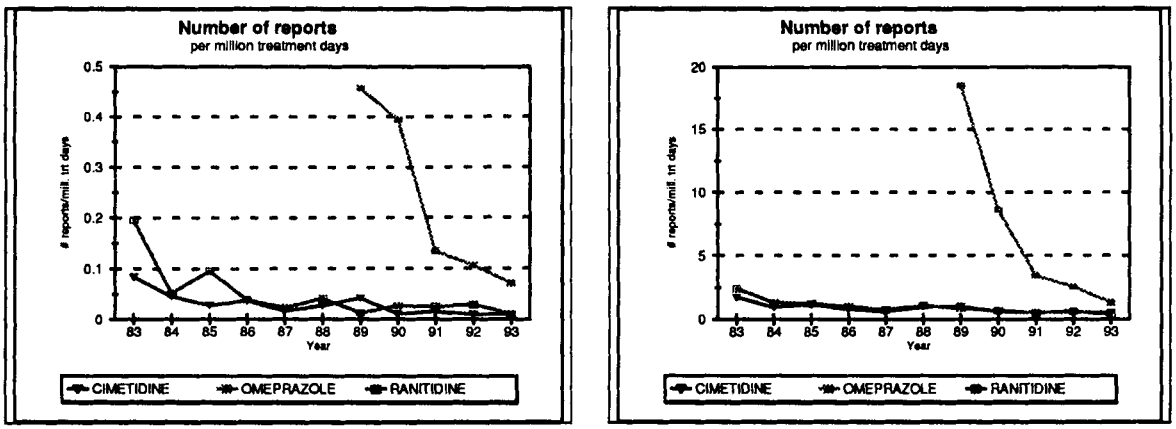

Fig. 1 — (a) Reporting rate of all vision disorders in Germany, UK and USA by year. (b) Reporting rate of all ADRs in all countries by year

global basis. It is the reports on omeprazole from Germany, nine out of a total of 14, that are mainly responsible in both ratios.

Fig. 1a gives the reporting rate of all vision disorders, including blindness and severe vision disorders, by year in the target countries. The high reporting rates for omeprazole in 1989, 1990 and 1991 represent three, 25 and 17 reports, respectively. The overall reporting rates of all ADRs to the three drugs in all countries are shown in Fig. 1b.

Table 3 shows that few cases of blindness and severe visual disturbances were reported in relationship to the three drugs in the target countries. These reports were scattered by country, year and drug. The maximum number of reports for omeprazole in one year was eight in Germany in 1993. Four of these cases were related to intravenous or 'systemic' use (the latter probably also intravenous). The sales of i.v. omeprazole in Germany in 1993 were 84.9 kg (4.25 million treatment days), giving a reporting rate of 0.94 for blindness/severe vision disorders. It should be noted that intravenous omeprazole was not available in the UK and USA and that the kilogram sales of the intravenous form accounts for 7.8% of the total German sales.

Until 1993, only four cases of any visual abnormality with omeprazole had been reported in Germany. In 1993, a total of 15 cases were reported (all routes), including the eight with severe reactions mentioned above. Fig. 1a shows

Table 3 — Number of reports of blindness/severe vision disorders in Germany, UK and USA by year

Drug	Country	Route	83	84	85	86	87	88	89	90	91	92	93
Omeprazole	GFR	IV											2
	GFR	PO											4
	GFR	SY										1	2
	UK	PO								1		1	
	USA	PO							1	2			
Cimetidine	GFR	PO		1									
	UK	PO	2	1		2							
	USA		2						1				
	USA	PO	2	3	1	1			2				
Ranitidine	UK				2								
	UK	PO			1			3	1	2		1	1
	USA											1	
	USA	PO		1		2	1	1		1		2	

that, notwithstanding these reports, the overall reporting rate for vision disorders associated with omeprazole fell.

The dose of omeprazole recorded on adverse reaction reports stating 'systemic' or i.v. use from Germany was 80 mg daily in the three (out of four) reports stating dose. The recommended dose in that country is 10–20 mg once daily for i.v. use. Also the doses of peroral omeprazole were high in Germany (mean 30, range 20–80 mg daily in five reports). Comparative data were: UK mean 23.5, range 20–60 (29 UK reports) and 20 mg daily in all reports from the USA.

Nearly all the reports of blindness described very sick patients mainly managed in intensive care units. In some cases, the omeprazole was used as a prophylaxis against stress ulceration, which is not an approved indication for the drug. Thus the use of intravenous omeprazole in Germany, which relates to the majority of the cases of severe visual disorder found, is anomalous in extent (compared with other countries), dose (relative to the recommended dose), and indication (in some cases).

Since vasculitis has been suggested as an aetiological factor in vision disorders related to omeprazole, the reporting rates for this disorder, in the target countries, were calculated for the three drugs. The rates were 0.012, 0.0057 and 0.0041 per million treatment days for omeprazole, cimetidine and ranitidine respectively.

DISCUSSION

The signal of blindness and severe vision disorders to a widely used drug such as omeprazole is important. Our data show that the reporting rate is low even using the worst case scenario, taking the numerator and denominator only from the countries where most reactions occurred. If there is a causal dose relationship, the high use of intravenous omeprazole, the higher doses, and perhaps even the way this dosage form was used in Germany compared with other countries may provide one explanation why this suspected ADR was first reported there. There are, however, plausible non-causal explanations.

There is an apparently seven times higher reporting rate of omeprazole related to severe vision disorders than with the comparator drugs. This higher reporting rate is most striking for i.v./systemic omeprazole at 0.94 reports per million treatment days, but is confined to one country (Germany) and one year (1993). The high doses (about 80 mg daily) used in the reported cases from Germany counsel caution in applying the DDD (20 mg daily) in determining reporting rates, particularly for the i.v. preparation (which was not used in the UK or USA). It is also interesting that the reports of less severe visual disorders to omeprazole increased that year, and that these were also reports from Germany, where the signal was first published. The pathophysiology mentioned in the 1993 reports from Germany was varied, or described by the vague term 'vision abnormal'. Publicity could therefore have influenced the reporting rate of coincidental visual problems for that (and subsequent) years, since no consistent pathophysiological syndrome was reported.

The occurrence, shown in Table 3, of similar small numbers of reports for cimetidine and ranitidine, as well as omeprazole, scattered by country and year, further suggests that it is the baseline level of severe vision disorders which is being reported.

The overall reporting rate of vision disorders is also higher for omeprazole. Weber showed that there was a higher reporting rate soon after a drug was marketed, which persisted for about two years before falling to a stable, lower level.[9,10] He suggested that these higher reporting rates early after marketing require that comparisons between drugs be performed for comparable periods in their marketed life. The fall of reporting rate for omeprazole both of vision disorders and general ADRs is striking (Fig. 1a, b). When omeprazole was first marketed there was a considerable debate over its safety[11,12] which might account for the very high initial reporting rate. It is clear that the phenomenon described by Weber does not seem to apply to ranitidine, however, which was launched in the early 80s. Fig. 1b shows an ADR reporting rate for ranitidine which was very close to that of cimetidine which had been marketed since the mid 70s. These data suggest that a high reporting rate shortly following the launch of a drug may not be universally applicable, and certainly may be very variable in extent.

Vasculitis has been proposed as a possible aetiology of the visual disorder, but the even lower reporting rate of vasculitis makes this hypothesis unlikely without any other supporting evidence. To date no drug has been reported to cause vasculitis of the optic nerve, let alone significant visual loss.

It is clear that this study has limitations in not assessing attributability whilst including cases with different aetiology. These errors would overestimate incidence whilst the well known underreporting in spontaneous reporting systems has the opposite effect. The reporting rate for omeprazole appears to be falling still, and again it should be emphasized that the maximum incidence of both general and visual ADRs is likely to be low, even assuming total attributability and probable underreporting.

A retrospective cohort study has been performed using the VAMP data base.[13] The incidence of vascular and inflammatory eye disorders was between 0 and 2.6 per 10,000 person-years for the drugs famotidine, nizatidine, omeprazole, cimetidine and ranitidine compared with a non-use incidence of 1.3. The conclusion of the study was that the oral use of the drugs was not associated with any increased risk in the UK (note that the intravenous form of omeprazole is not available in the UK). The possible inclusion of person-time without exposure to the drug, due to failure of compliance or not otherwise taking the drugs according to the end-points described, might lead to an underestimate of incidence in the VAMP study. An assumption that the DDD is the mean daily dose for the reporting rates in our study also could lead to a false estimate due to a variety of competing factors. It would be unwise to compare rates in the two studies too closely in view of the different assumptions made. The present study adds to the picture in giving an international and chronological perspective of the issue, supporting the view that there is no relationship between oral omeprazole use and visual disorders.

One reasonable alternative explanation for the cases reported in relationship to omeprazole is that they were a result of severe clinical illness. Apart from the well known causes of AION such as arteritis, diabetes, hypertension and atherosclerosis,[14] acute blood loss may be a cause,[15–17] as may pancreatitis[18] and burns[19] and recent studies on ocular circulation show that the supine position may have a deleterious effect on ocular perfusion.[20] Acute blood loss and recumbency may be of relevance to patients treated by omeprazole in an emergency situation and exploration of this possibility seems to be of clinical importance. A study of severe visual abnormalities following the management of severe illness in intensive care units would be of great medical interest.

This paper demonstrates the huge problem which faces decision makers with a cluster of spontaneous reports of a possibly rare but severe adverse reaction to a widely used drug. An analysis of case reports is very difficult in the absence of good background information on the incidence and pathophysiology of the event. In this case the wide use of the drug made it likely that many randomly associated events would be reported and the unusual reporting pattern related to publicity further complicated the issue. It is difficult, based on the apparent rare incidence to agree with Kimbel,[21] that it would be cost effective for the manufacturer 'to do his homework to elucidate the mechanism of a suspected adverse reaction'.

We have shown that the combined WHO and IMS data gives a much clearer picture of this important drug-ADR signal. The data have given an indication of the likely low public health risk based on international experience, and outlined possibilities other than a true causal relationship. The aim of the WHO Collaborating Centre and IMS project (ASAP), is to be able to provide a very rapid picture of international ADR reports set against the pattern of drug use and demographic information in countries with data relevant to any signal.

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REFERENCES

1. Anon. Omeprazol (Antra) parenteral: sehstörungen und blindheit? Arznei-telegram, p. 74: 7/1993 publ. Institut für Arzneimittelinformation, Berlin, Germany.
2. Anon. Omeprazol und sehstörungen. Bundesgesundhbl., p. 293: 7/1993 publ. Bundesgesundheitsamt, Germany.
3. Anon. Omeprazol und sehstörungen. *Deutsches Ärzteblatt* 1993; **90**: C1439–C1440.
4. Anon. Omeprazo-haltige arzneimittel. *Deutsche Apotheker Zeitung* 1994; **134**/9: 710.

5. Anon. Omeprazole injection to be withdrawn in Germany? *SCRIP* 1994; **1904**: 22.
6. Schönhöfer, P. Intravenous omeprazole and blindness. *Lancet* 1994; **343**: (8898) 665.
7. Creutzfeldt, W. C. and Blum, A. L. Safety of omeprazole. *Lancet* 1994; **343**: (8905) 1098.
8. Albel, M. Tysk specialist slår larm om Losec-Losec kan orsaka blindhet. *Länstidningen* 1994; **70**: 1 and 4.
9. Weber, J. C. P. Epidemiology of adverse reactions to non-steroidal anti-inflammatory drugs. In: *Side Effects of Anti-inflammatory/Analgesic Drugs*, Vol. 6. Rainsford, K. D. and Velo, G. (Eds), Raven Press, New York, 1984, pp. 1–7.
10. Weber, J. C. P. Mathematical models in adverse drug reaction assessment. In: *Latrogenic Diseases*, 3rd. ed. D'Arcy, P. F. and Griffin, J. P. (Eds), Oxford University Press, 1986, pp. 102–107.
11. Dukes, M. N. G. Gastrointestinal drugs: omeprazole. In: *Side Effects of Drugs Annual, 14*. Dukes, M. N. G. and Beeley, L. (Eds), Elsevier, Amsterdam, 1990, p. 319.
12. Langman, M. J. S. Gastrointestinal drugs: omeprazole. In: *Meyler's Side Effects of Drugs*, 12th ed. Dukes, M. N. G. (Ed.), Elsevier, Amsterdam, 1992, pp. 943–944.
13. Rodríguez, L. A. G., Mannino, S. and Wallander, M.-A. Ocular safety of antiulcer drugs. *Lancet* 1995; **345**: (8956) 1059–1060.
14. Cerovski, C. and Saric, S. Risk factors in non-arteritic anterior optic neuropathy. *Acta Medica Iugoslavica*. 1990; **44**(5): 533–540.
15. Chisholm, I. A. Optic neuropathy of recurrent blood loss. *British Journal of Ophthalmology* 1969; **53**: 289–295.
16. Ballen, P. H., Fox, M. J. and Weissman, G. S. Ischemic optic neuropathy secondary to intestinal hemorrhage. *Annals of Ophthalmology* 1985; **17**: 486–488.
17. Sharma, R. and Desai, S. Postpartum hemorrhage producing acute ischemic optic neuropathy. *Asia Oceania Journal of Obstetrics and Gynaecology* 1993; **19**(3): 249–251.
18. Steel, J. R., Cockcroft, J. R. and Ritter, J. M. Blind drunk: alcoholic pancreatitis and loss of vision. *Postgraduate Medical Journal* 1993; **69**: 151–152.
19. Xiao, J., Xu H. and Kong, F. Y. Bilateral visual loss after severe burns in a child. *Burns* 1991; **17**(5): 423–424.
20. James, C. B. and Smith, S. E. The effect of posture on the intraocular pressure and pulsatile ocular blood flow in patients with non-arteritic anterior ischaemic optic neuropathy. *Eye (England)* 1991; **5**(3): 309–314.
21. Kimbel, K. H. Suspension of licence for intravenous omeprazole in Germany. *Lancet* 1994; **344**: (8924) 756.

