about £25 000. Whereas the cost per life year gained of £8000 for a five yearly interval may be considered acceptable, the marginal costs per life year gained by screening every three years are high in comparison with the costs of many other health care facilities. In addition, we found that increasing the screening frequency will worsen the balance between favourable and adverse health effects (unnecessary treatment of women with false positive results and regressive lesions) of screening.[11]

Our analysis is based on published data from studies that are now more than 10 years old. Reports of an increasing incidence and mortality, especially in younger women, do not influence our results since our estimates are predominantly determined by the duration of preinvasive stages and the sensitivity of the screening test. These factors could also change over time,[12] stressing the need for continuous re-evaluation of the protection afforded by negative smear test results.

Conclusion

The most serious negative effects of cervical cancer are early death and the serious morbidity associated with advanced disease. Therefore, reduction of the risk of death from cervical cancer should be the primary criterion in evaluating screening policies. Reduction in incidence of invasive cancer carries an additional benefit since some major therapeutic procedures and their associated morbidity will be avoided, but this should be considered in conjunction with the negative health effects of diagnostic and therapeutic procedures that are induced by screening.[11]

The use of reduction in incidence as a proxy for reduction in mortality is appealing. However, we have shown that protection against invasive cancer underestimates protection against mortality. The two criteria will lead to different recommendations: screening intervals based on mortality are about 50% longer than those based on incidence. This difference is caused by the good survival of women with screen detected invasive cancers.

On the basis of our calculations of the reduction in cervical cancer mortality we conclude that screening intervals of five years are appropriate. Regular screening at this interval in the age group 35-64 is expected to give about 90% reduction in the risk of dying from cervical cancer. More intensive screening will give little additional benefit, and should be discouraged in view of the adverse effects and the high costs.

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Endocrine adverse effects of omeprazole

Marie Lindquist, I Ralph Edwards

WHO Collaborating Centre for International Drug Monitoring, Box 26, S-751 03 Uppsala, Sweden
Marie Lindquist, *senior pharmaceutical officer*
I Ralph Edwards, *medical director*

Correspondence to:
Ms Lindquist.

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Omeprazole is thought to act to reduce gastric acid through specific binding to the parietal cell proton pump hydrogen ion potassium ATPase. Selectivity is further strengthened by the drug's basic nature causing it to accumulate in acid spaces, where it is activated. Both cimetidine and ranitidine have been reported to cause gynaecomastia and impotence, though, unlike cimetidine, ranitidine does not bind to androgen receptors. There have been two single case reports of gynaecomastia during treatment with omeprazole.[1,2] We add further cases and also record cases of impotence related to omeprazole. All had been reported within the World Health Organisation's programme for international drug monitoring as cases, and in all cases causality seemed possible.

Case histories

The cases represent the total reported experience of these adverse drug reactions up to December 1991. There were 15 cases of impotence and 15 of gynaecomastia or breast enlargement.

Impotence—All cases of impotence were in men (mean age 52·6 years). They had been taking 20-40 mg omeprazole daily for a mean of four days (cases in which exact dates were recorded only) before onset. Other drugs were not reported in eight cases and not used in three. The treated condition was mostly reflux oesophagitis (12 cases). Full details of patients are given in the table.

Gynaecomastia or breast enlargement—Gynaecomastia occurred in 13 men (mean age of 56·8 years), and breast enlargement occurred in two women aged 41 and 77. The doses of omeprazole used were 20 mg daily in most patients, 40 mg daily in two men, 60 mg daily in one man, and either unknown or intermittent in three patients, including one woman. The mean time to onset (known in 12 cases) was 2·9 months. Most of the patients had either gastric or duodenal ulceration, only three having oesophagitis. In three cases the diagnosis was not recorded. One patient had the Zollinger-Ellison syndrome. The table gives details of the patients.

Comment

There have been two single case reports of gynaecomastia in patients taking omeprazole but none of impotence. Both reports point out that the mechanism for the gynaecomastia is not apparent from the pharmacology of the drug. The cases we report are further evidence of the adverse reaction and come from eight different countries. Furthermore, they include the hitherto unrecorded adverse effect of impotence. Confounding due to other disease or other drugs

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Case descriptions of patients with impotence and gynaecomastia associated with omeprazole

Case No	Age and sex	Reaction	Report source	Onset date	Dose	Duration	Indication	Other drugs	Outcome
1	59 M	Impotence, libido decreased, gastritis	Specialist doctor	Jan 1988	20 mg Daily	Unknown	Oesophageal disease	Metoclopramide	Not recovered when reported
2	49 M	Impotence	General practitioner	Unknown	1 Dosage form daily	10 Days	Gastric ulcer	None stated	Recovered
3	44 M	Impotence (erection failure)	Hospital	Mar 1990	20 mg Daily	6 Days	Chronic oesophagitis	Sodium alginate/antacids	Recovered
4	67 M	Impotence (erection failure)	General practitioner	June 1990	20 mg Weekly	2 Days	Duodenal ulcer	None stated	Recovered
5	59 M	Impotence (erection failure), flushing	General practitioner	Feb 1990	20 mg Daily	1 Day	Oesophagitis	None stated	Unknown
6	49 M	Impotence, libido decreased	Unknown	Feb 1990	20 mg Daily	<1 Month	Peptic ulcer	None stated	Unknown
7	39 M	Impotence	Unknown	Feb 1990	40 mg Daily	<1 Month	Reflux oesophagitis	None stated	Unknown
8	57 M	Impotence	Manufacturer	Jan 1990	20 mg Daily	1 Day	Resistant oesophagitis	None stated	Recovered
9	49 M	Impotence (2nd degree erection failure)	General practitioner	May 1990	20 mg Daily	<1 Month	Reflux oesophagitis	None stated	Not recovered when reported
10	49 M	Impotence (erectile)	Unknown	Nov 1990	20 mg Daily	2 Days	Reflux oesophagitis	None stated	Unknown
11	65 M	Impotence	General practitioner	Dec 1990	20 mg Daily	5 Days	Oesophagitis	Metoclopramide, sodium alginate/antacids	50% Improvement after stopping drug
12	56 M	Impotence	General practitioner	Jan 1991	20 mg Daily	<20 Days	Oesophagitis	Lisinopril, bendrofluazide	Unknown
13	60 M	Impotence	Doctor via manufacturer	Unknown	20 mg Daily	Unknown	Severe reflux	None	Recovered
14	34 M	Impotence, libido decreased	Doctor	Feb 1990	20 mg Daily	8 Days	Barrett's oesophagitis	None	Unknown
15	53 M	Impotence	General practitioner	May 1990	20 mg Daily	1 Day	Oesophageal reflux	None	Recovered
16	38 M	Gynaecomastia, weight increase, diarrhoea	Clinical trial	Oct 1988	1 Dosage form daily	2 Months	Intractable ulcer	Cholestyramine	Not recovered when reported
17	76 M	Gynaecomastia (unilateral, tender)	Hospital	Feb 1989	20 mg Daily	7 Months	Duodenal ulcer	Digoxin, aspirin	Recovered
18	37 M	Gynaecomastia (right, tender)	Unknown	Aug 1989	40 mg Daily	1 Month	Stomach ulcer	Clofibrate, probucol, ergotamine	Not recovered when reported
19	65 M	Gynaecomastia (left, tender)	Doctor	Sept 1990	20 mg Daily	5 Months	Bleeding duodenal ulcer	Prednisone, sulphasalazine, calcium carbonate, theophylline, salbutamol, triamterene/hydrochlorothiazide	Recovered
20	75 M	Gynaecomastia	Unknown	Unknown	20 mg Daily	Unknown	Unknown	None stated	Not recovered when reported
21	68 M	Gynaecomastia	General practitioner	Jan 1989	20 mg Daily	Unknown	Gastric ulcer	None stated	Not recovered when reported
22	55 M	Gynaecomastia (left, tender)	General practitioner	Dec 1989	40 mg Daily	3 Months	Ventricular ulcer	None stated	Not recovered when reported
23	71 M	Gynaecomastia (left)	General practitioner	Jan 1990	20 mg Daily	1 Month	Ventricular ulcer	Ketoprofen	Recovered
24	44 M	Gynaecomastia (painful)	Unknown	Sept 1989	60 mg Daily	2 Months	Zollinger-Ellison syndrome	None stated	Not recovered when reported
25	74 M	Gynaecomastia (tender)	General practitioner	Nov 1989	20 mg Daily	23 Days	Oesophagitis	Cimetidine. For some years: spironolactone, salbutamol, beclomethasone, aspirin, nifedipine, isosorbide	Not recovered when reported
26	77 F	Gynaecomastia, warfarin sensitivity	Specialist doctor	Dec 1989	20 mg Daily	6 Days	Unknown	Warfarin, digoxin, amiloride/frusemide	Less noticeable Feb 5
27	41 F	Gynaecomastia	Manufacturer	April 1990	Unknown	Unknown	Unknown	None	Unknown
28	35 M	Gynaecomastia	Unknown	June 1990	20 mg Daily	1 Month	Bleeding duodenal ulcer	Ranitidine (until omeprazole was started 11 June)	Unknown
29	35 M	Gynaecomastia (left)	Unknown	July 1990	Intermittent	8 Months	Resistant gastro-oesophageal reflux	None	Resolving when reported
30	65 M	Gynaecomastia	Doctor via manufacturer	Nov 1989	Intermittent	3 Months	Oesophageal reflux	None	Not recovered when reported

*Patient had taken Tagamet (cimetidine) for some time before omeprazole; never any gynaecomastia with Tagamet.

seemed unlikely in 14 of the patients with adequate information to make a judgment.

The relation of cimetidine to gynaecomastia and impotence is explicable pharmacologically, but ranitidine has also been incriminated in a few cases. A pertinent question is therefore whether the treated disease may be implicated. Severe liver disease, in which gynaecomastia and impotence may feature, is associated with a high incidence of peptic ulceration but is unlikely to go unrecognised in so many reports. Increased prolactin concentrations occur in Wermer's syndrome (multiple endocrine neoplasia, type I) as well as peptic ulceration, but in the cases of gynaecomastia and impotence associated with omeprazole reported to date prolactin and other relevant hormone concentrations were normal. Inhibition of cytochrome *P*-450 as postulated for gynaecomastia and impotence caused by cimetidine is possible also in the case of omeprazole as it too has some properties inhibiting liver cytochrome *P*-450 enzyme.[3,4]

That seven of the patients with impotence and five of those with gynaecomastia either had recovered or were improving at the time of this report is strong evidence that omeprazole was the causative agent.

These cases occurred in several countries participating in the WHO collaborative programme, and the information was gained and assessed in different ways. Causality cannot therefore be simply determined from the information available, and our conclusion does not necessarily represent the opinion of the WHO.

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