Clinical implications

- Over 50% of menopausal women suffer from distressing vasomotor symptoms, whose exact cause remains unclear
- Oestrogen replacement is effective treatment for most women, but effective non-hormonal alternatives are required for those averse to taking oestrogen or in whom oestrogen is contraindicated
- Evening primrose oil is a rich source of gamolenic acid, popularly believed to suppress menopausal flushing
- This study showed that evening primrose oil had no benefit over placebo in the alleviation of vasomotor symptoms
- Given these results and the lack of a scientific reason for using gamolenic acid, the use of evening primrose oil in treating menopausal flushing cannot be supported

may be because metabolites of evening primrose oil provide high concentrations of prostaglandins which decrease the affinity of ligands such as oestrogens and other hormones for their receptors.[12] In addition, several experiments have shown prostaglandins acting at the hypothalamus stimulate the release of follicle stimulating hormone and luteinising hormone.[5] High concentrations of these pituitary gonadotrophins have long been implicated in the production of menopausal vasomotor disorders, although the exact mechanism remains elusive. Based on the data from this small pilot study and on the lack of a hypothetical rationale for using gamolenic acid, we cannot support the use of evening primrose oil in the treatment of menopausal hot flushes. Larger studies are required.

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Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs

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Abstract

***Objective*—To study the risk of gynaecomastia associated with cimetidine, misoprostol, omeprazole and ranitidine.**

***Design*—Open cohort study with nested case-control analysis.**

***Setting*—General practices in United Kingdom that had computerised offices, 1989-92.**

***Subjects*—81 535 men aged 25-84 years who received at least one prescription for cimetidine, misoprostol, omeprazole, or ranitidine during the study period.**

***Main outcome measures*—New occurrences of idiopathic gynaecomastia diagnosed by general practitioner.**

***Results*—The relative risk of gynaecomastia for current users of cimetidine compared with non-users was 7·2 (95% confidence interval 4·5 to 11·3). Relative risks for misoprostol, omeprazole, and ranitidine were 2·0 (0·1 to 10·7), 0·6 (0·1 to 3·3), and 1·5 (0·8 to 2·6), respectively. Current users of cimetidine on a daily dose ≥1000 mg had more than 40 times the risk of developing gynaecomastia than non-users. The period of highest risk was seven to 12 months after starting cimetidine treatment. Spironolactone (relative risk 9·3 (3·3 to 26·1)) and verapamil (9·7 (2·6 to 36·0)) were associated with a relative risk of gynaecomastia comparable to one for cimetidine.**

***Conclusions*—Use of cimetidine, but not the three other antiulcer drugs, is associated with a substantially greater risk of gynaecomastia in men. A strong dose-response relation was present among cimetidine users.**

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Introduction

Gynaecomastia (enlargement of true breast tissue as opposed to adipose tissue) was a common clinical finding in case series.[1-3] The differential diagnosis of gynaecomastia depends on physiological and pathological criteria, and pathological gynaecomastia can be further classified into that associated with other medical conditions and idiopathic gynaecomastia. Cimetidine has repeatedly been reported as causing gynaecomastia,[4-7] and ranitidine was associated with gynaecomastia in a single case.[8] More recently omeprazole, a proton pump inhibitor also used as an ulcer healing drug, has been associated in more than a dozen cases with the development of gynaecomastia.[9-11] No epidemiological study has been published comparing the incidence of gynaecomastia among the various ulcer healing drugs. We performed a large population based cohort study which provides estimates of the absolute and relative risk of idiopathic gynaecomastia in patients who received cimetidine, misoprostol, omeprazole, or ranitidine, four drugs used primarily for treating peptic ulcer disease. The results are based on information held on British general practitioners' computers.

Methods

Over four million residents in the United Kingdom are enrolled with selected general practitioners who use office computers provided by Value Added Medical Products (VAMP) Research and have agreed to provide data for research purposes. They record medical information in a standard manner and supply it

anonymously to VAMP Research on an ongoing basis. Among other items, the recorded information includes the patient's characteristics, medical diagnoses and comments arising from the patient's visit to the general practitioner, referral letters from consultants, and details of stays in hospital. Also, the general practitioners generate prescriptions directly with the computer, and these drugs are automatically transcribed into the patient's computer record. A distinctive attribute of this computerised medical information system is that the general practitioner is asked to provide the indication for each new course of medication. A modification of the Oxford Medical Information System classification is used to enter medical diagnoses, and a coded drug dictionary based on the Prescription Pricing Authority's dictionary is used for the recording of prescriptions. Two recent validation studies determined that information from manual medical records in the general practitioners' offices was recorded on the computer over 90% of the time.[12 13]

Study population—For this study, 478 practices contributed information from 1 January 1989 through 15 September 1992. Men between 25 and 81 years old in 1989 and registered with one of these practices entered the study population when they were prescribed cimetidine, misoprostol, omeprazole, or ranitidine during the study period. Men with a history of gynaecomastia before they received one of these drugs during the study period were excluded, as were those with Klinefelter syndrome, testicular cancer, breast cancer, or liver disease or who had used replacement androgen therapy. A total of 81 535 men formed the final study population and were followed until either the first occurrence of gynaecomastia, any malignant neoplasm, liver disease, a diagnosis of alcoholism, use of replacement androgen therapy, transfer to another practice, death, or 15 September 1992, whichever came first (table 1).

Exposure definition—Thirty days was the most common duration of an antiulcer prescription, accounting for 72% of all prescriptions; 60 days was the second most common duration, accounting for 15% of all prescriptions. Person time was aggregated across calendar time and age groups into two mutually exclusive time windows for each of the four drugs: "current use," starting from day 1 of each prescription until the earlier of day 60 or the date of the next prescription; and "past use," from day 61 of each prescription until the earlier of day 120 or the date of the next prescription. The person time beginning from day 120 after each prescription for any ulcer healing drug and continuing until any subsequent prescription was combined into a "non-use" category. Duration of use was defined as the number of consecutive prescriptions (that is, prescriptions that followed within a maximum of 60 days of the same ulcer healing drug) among current users. Duration was categorised as "unknown" when there were less than six months' data in the automated prescription file. Daily dose was estimated according to the strength prescribed and the prescription's instructions as recorded on the computer.

Case ascertainment—We identified among the study population 160 subjects who had a first time diagnosis of gynaecomastia. We reviewed their computerised profiles without knowing their drug use and eliminated six with clear concurrent causes for their breast enlargement (liver disease, two; cancer, three; or trauma, one). To validate the diagnosis of gynaecomastia recorded on a computer for a random sample of half of the 160 subjects, we sent the general practitioners a questionnaire requesting details of some of the clinical features and any correspondence available related to the diagnosis of interest (referral letters, discharge letters). All patients' personal identifiers were suppressed before any material was sent to us. We excluded only one additional patient (trauma) after reviewing the information on these 80 patients.

Cohort analysis—We calculated standardised rates of gynaecomastia for each antiulcer drug, using as an internal standard the distribution of person time for the total study population over categories of calendar time and age groups. We also performed Poisson regression with the generalised linear interactive modelling (GLIM) package[14] and obtained similar results.

Nested case-control analysis—A random index date between 1 January 1989 and 15 September 1992 was assigned for each of the 81 535 study members. If the random date of a study member were included in his eligible time at risk (from study entry to end of follow up), we considered the person as an eligible control.[15] From the list of eligible controls, we selected a random sample of 1000 controls and compared them with the 153 cases. We used unconditional logistic regression to estimate the relative risk and 95% confidence interval for gynaecomastia within each category of exposure to ulcer healing drugs, using the non-user group as the reference group. We examined duration-response and dose-response relations among current users of cimetidine and we calculated relative risks for other selected drugs implicated in the literature as causing gynaecomastia (box).

Drugs associated with gynaecomastia

Antibiotics:
- Isoniazid
- Ketoconazole
- Metronidazole
- Miconazole

Cardiovascular drugs:
- Atenolol
- Captopril
- Digoxin
- Enalapril
- Methyldopa
- Nifedipine
- Spironolactone
- Verapamil

Psychoactive drugs:
- Diazepam
- Tricyclic antidepressants

Results

In all, 153 men presented with a first occurrence of idiopathic gynaecomastia. Table II presents a summary of the clinical features for the 80 patients for whom we received general practitioners' medical reports. In 12 patients the gynaecomastia did not regress, and five underwent a subareolar mastectomy. In none of the cases was a diagnosis of any other endocrine changes, such as impotence, recorded on computer.

The incidence for age and calendar time standardised among non-users and current users of the four antiulcer drugs is shown in table III. Only cimetidine users had a substantially greater risk of gynaecomastia than non-users: the relative risk associated with current use of cimetidine was 7·2 (95% confidence interval 4·5 to 11·3). The risk among users of the three other antiulcer drugs was not greatly different from the risk among non-users. These estimates of relative risk were virtually identical to the ones obtained in the nested case-control analysis.

Table IV presents the risk among current users of

TABLE I—*Prescriptions for ulcer healing drugs in study population. Values are numbers (percentages)*

Drug	No of patients* (n=81 535)	No of prescriptions (n=585 134)	Age distribution of patients receiving prescriptions			
			25-39 69 291 (11·8)	40-54 140 607 (24·0)	55-69 223 892 (38·3)	70-84 151 344 (25·9)
Cimetidine	37 202	215 191	25 388 (11·8)	51 668 (24·0)	83 591 (38·8)	54 544 (25·3)
Misoprostol	2 663	9 196	682 (7·4)	2 221 (24·2)	3 794 (41·3)	2 499 (27·2)
Omeprazole	9 972	33 503	5 026 (15·0)	8 580 (25·6)	12 253 (36·6)	7 644 (22·8)
Ranitidine	45 674	327 244	38 195 (11·7)	78 138 (23·9)	124 254 (38·0)	86 657 (26·5)

*Receiving at least one prescription for any of the four ulcer healing drugs. About 16% of the study subjects received more than one drug during the study.

cimetidine broken according to duration of treatment, daily dose, and the joint effects between increasing duration and increasing daily dose. The period at highest risk seemed to be between the seventh and 12th month after starting treatment with cimetidine. Dose was also a major predictor of the occurrence of gynaecomastia, with most of the risk associated with ⩾1000 mg daily. There was a strong synergy of effects between the duration and dose of cimetidine. When we used a common reference group (patients who received six or fewer prescriptions for cimetidine at a dose of 800 mg or less) we found relative risks of 2·0 in those who received seven or more prescriptions at a dose of 800 mg or less, 4·2 in those receiving six or fewer prescriptions at a dose of 1000 mg or more, and 13·1 in those receiving seven or more prescriptions at a dose of 1000 mg or more.[16] The excess relative risk due to interaction between an increasing duration and an increasing dose was 7·9; owing to the small numbers in each group, this estimate of interaction presented some statistical uncertainty.[17] The proportion of gynaecomastia among current users of cimetidine with both long term prescriptions and high daily doses, due to their synergistic effect, was 60%.

Spironolactone (relative risk 9·3 (3·3 to 26·1)) and verapamil (9·7 (2·6 to 36·0)) were the only two drugs associated with a risk of gynaecomastia comparable in magnitude with the one for cimetidine (table V).

TABLE II—*Clinical features of cases of gynaecomastia**

Finding	No (%) of patients
Clinical presentation:	
Self reported	67 (84)
Incidental finding	11 (14)
Unknown	2 (2)
Site:	
Unilateral:	34 (43)
Left	12 (15)
Right	12 (15)
Unknown	10 (13)
Bilateral	38 (47)
Unknown	8 (10)
Patient referred to consultant or hospital:	
No	55 (69)
Yes	21 (26)
Unknown	4 (5)
Regression:	
Complete	37 (46)
Partial	14 (18)
None	12 (15)
Unknown	17 (21)

*Based on 80 patients with medical records. The patient excluded after review of medical records had a self reported presentation in the right breast site. He was referred and the regression status was unknown.

TABLE III—*Incidence and relative risk of gynaecomastia among non-users and current users of ulcer healing drugs*

	Person years	No of cases* (n=153)	Incidence (per 1000 person years)†	Relative risk (95% confidence interval)
Non-users	55 763	24	0·46	1·0
Cimetidine	24 056	86	3·29	7·2 (4·5 to 11·3)
Misoprostol	967	1	0·74	2·0 (0·1 to 10·7)
Omeprazole	3 386	1	0·25	0·6 (0·1 to 3·3)
Ranitidine	35 133	26	0·69	1·5 (0·8 to 2·6)

*15 cases that occurred during past use of one of these drugs.
†Standardised rates for age and calendar year.

TABLE IV—*Influence of duration and daily dose of cimetidine on risk of gynaecomastia among current users*

	No of cases (n=153)	No of controls (n=1000)	Relative risk* (95% confidence interval)
Duration (No of prescriptions):			
1-3	14	52	3·9 (2·0 to 7·7)
4-6	10	17	7·0 (2·9 to 16·6)
7-12	27	28	14·3 (7·6 to 26·9)
⩾13	22	40	6·5 (3·5 to 12·2)
Unknown	13	32	6·2 (2·8 to 13·6)
Daily dose (mg):			
⩽600	18	64	3·4 (1·8 to 6·4)
601-999	52	100	7·7 (4·8 to 12·3)
⩾1000	16	5	43·5 (14·8 to 127·3)
Duration (No of prescriptions) and daily dose (mg):			
1-6; <1000	20	66	4·1 (2·3 to 7·5)
⩾7; <1000	40	66	8·1 (4·9 to 13·4)
1-6; ⩾1000	4	3	18·3 (3·8 to 87·9)
⩾7; ⩾1000	9	2	54·7 (11·2 to 267·3)
Unknown	13	32	6·1 (2·8 to 13·4)

*From unconditional logistic regression models including the categories of exposure listed, age, and calendar year by comparison with non-users.

Clinical implications

- Idiopathic gynaecomastia has been reported with many drugs, including cimetidine
- No epidemiological study has examined the risk of gynaecomastia associated with various antiulcer medications
- This study shows that use of cimetidine is associated with clinically important gynaecomastia but that use of misoprostol, omeprazole, and ranitidine is not
- A strong dose-response relation is shown with use of cimetidine
- Spironolactone and verapamil also present a large increased risk of developing gynaecomastia

TABLE V—*Relative risk of gynaecomastia associated with current use of certain drugs*

	No of cases (n=153)	No of controls (n=1000)	Relative risk* (95% confidence interval)
Digoxin	11	18	2·7 (1·2 to 6·1)
Nifedipine	18	38	2·9 (1·6 to 5·3)
Spironolactone	11	6	9·3 (3·3 to 26·1)
Verapamil	6	4	9·7 (2·6 to 36·0)

*From unconditional logistic regression models including the drugs listed, age, and calendar year by comparison with non-users.

Discussion

These results indicate that use of cimetidine is associated with clinically important idiopathic gynaecomastia but that the use of misoprostol, omeprazole, and ranitidine is not. Clinical trials found that up to 0·8% of the subjects exposed to high doses of cimetidine developed gynaecomastia.[5] In our study population there were close to 2000 men who took 1000 mg a day or more; 15 went on to develop gynaecomastia. Despite the obvious differences between the two studies, especially with respect to surveillance of the subjects, estimates of risk for cimetidine are closely comparable, indicating that our source of information and study design had adequate validity to assess this outcome.

A recent publication presented a case series of endocrine adverse effects associated with omeprazole reported to the World Health Organisation Collaborating Centre for International Drug Monitoring.[11] The authors suggest that omeprazole causes impotence and gynaecomastia. Our study did not examine the risk of impotence. However, there is no indication in the present study that use of omeprazole is associated with a greatly increased risk for gynaecomastia.

The mechanism by which cimetidine causes gynaecomastia has been discussed by Galbraith and Michnovicz, who showed that giving cimetidine to normal volunteers decreases 2-hydroxylation of oestradiol resulting in an increase in the serum oestradiol concentration.[18] In contrast, ranitidine did not affect 2-hydroxylation nor did omeprazole.[19] Our results are in agreement with these biochemical findings.

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Use of antidepressants among people committing suicide in Sweden

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Abstract

***Objective*—To analyse the outcome of depression in the Swedish population as reflected by the detection of antidepressants in a national forensic toxicological screening programme of unnatural deaths.**

***Design*—Antidepressants detected by the National Laboratory of Forensic Chemistry were related to data on use expressed in person years of exposure.**

***Subjects*—All 7000 cases of unnatural death with results from forensic toxicological screening in 1990-1; this included 3400 (85%) of the 4000 cases of suicide in Sweden.**

***Main outcome measures*—Number of findings of antidepressants in the screening programme and number of findings of different antidepressants in relation to their use.**

***Results*—Antidepressants were found in 585 screening tests, corresponding to 542 subjects or less than 16% of the 3400 cases of suicide. Newer, less toxic antidepressants were found more often than the older compounds. Toxic concentrations of antidepressants were found in only 190 cases (5·6%).**

***Conclusion*—A consistent finding in surveys of suicide is that about half of the patients who commit suicide are depressed. The current data suggest that most depressed patients who commit suicide are not taking antidepressants immediately before death. Therapeutic failure may be a greater problem with antidepressants than toxicity as the results did not indicate any advantage of the newer, less toxic antidepressants. All causes of death should be included in risk analyses, thereby providing an estimate of effectiveness as well as toxicity of antidepressants.**

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Introduction

There is a strong relation between suicide and depression, but the availability of effective antidepressants has not substantially lowered the incidence of suicide.[1-4] Several factors may contribute to this. Firstly, depression is often wrongly diagnosed or inadequately treated[1,5,6]; secondly, traditional antidepressants often have side effects, and compliance with the treatment is therefore low[7]; and, thirdly, antidepressants are toxic drugs and may be used to commit suicide.[8-10]

The toxicity of the classic tricyclic antidepressants in overdose has been referred to as a marketing argument for newer and less toxic antidepressants. The efficacy of these new drugs relative to tricyclics, however, is debatable.[11] With a national health insurance scheme covering all 8·6 million inhabitants and with all pharmacies run by the National Corporation of Pharmacies, Sweden provides a good opportunity for pharmacoepidemiological studies. As the Swedish screening programme for forensic toxicology covers practically all suicides we decided to analyse the outcome of depression in the population as reflected by the detection of different antidepressants in this screening programme.

Subjects and methods

Unnatural deaths are handled by the National Board of Forensic Medicine in any of six regional units in Sweden. Cases of suspected or obvious suicide are routinely screened for about 200 substances including medicines, illegal drugs, and alcohol at one laboratory, the National Laboratory of Forensic Chemistry in Linköping. This is routinely done from the three major regional units covering 62% of all cases of suicide, but in one region only about two thirds of cases were subject to forensic toxicological screening. Thus of all suicides in 1990-1, 85% were subject to such screening. Blood samples, usually taken from the femoral vein at necropsy, are analysed by using headspace gas chromatography and capillary gas chromatography with nitrogen specific detector.[12] The screening procedure is primarily focused on finding drugs in toxic concentrations. Antidepressants, however, will be detected at blood concentrations in the therapeutic range (above 0·2-0·4 μmol/l). The results are stored on a computerised database from which we obtained the number of screenings (and concentrations) at which each antidepressant had been detected. All antidepressants available in Sweden were covered by these toxicological screenings and thus included in the study (except selective serotonin reuptake inhibitors, which were introduced during 1990-1 and then had a minimal share of the market). Results are, however, given for only the nine major antidepressants, covering 98% of the sales (table I).

Nortriptyline was considered to be a metabolite and not counted when the parent drug amitriptyline was found in the same blood sample. Desipramine was