SHORT COMMUNICATION

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Gynaecomastia Associated with Proton Pump Inhibitors

A Case Series from the Spanish Pharmacovigilance System

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Abstract

Objective: Proton pump inhibitors (PPIs) are widely used in the management of peptic ulcer and related symptoms. They have been linked to certain endocrine adverse reactions, including gynaecomastia. The aim of the present study is to investigate the association between the use of PPIs and the development of gynaecomastia.

Methods: Reports of cases of gynaecomastia that had putatively been induced by PPIs and that had been collected by the Spanish Pharmacovigilance System via the 'yellow card' scheme, were analysed. Reporting odds ratios (RORs) were calculated as a measure of disproportionality.

Results: Twenty-four cases of gynaecomastia associated with PPIs were identified in the database of the Spanish Pharmacovigilance System. Overall, there was a clear temporal sequence of events in all cases and the adverse effect disappeared after drug withdrawal in most of the cases; 14 patients were also receiving other drugs at the time of the adverse effect. The ROR for omeprazole exposure versus no exposure, but not that for other PPIs, showed a statistically significant elevation (ROR adjusted for age 5.23; 95% CI 3.32, 8.26).

Conclusion: Considering the widespread use of PPIs, gynaecomastia may affect a large number of patients. In most cases, the condition seems to be reversible with drug withdrawal. Doctors should be aware of this potential adverse reaction when prescribing PPIs to their patients over long periods of time.

Proton pump inhibitors (PPIs) are effective suppressors of gastric acid secretion and, accordingly, they are broadly used in the management of peptic ulcer and other related symptoms; as a class, antiulcer drugs have remained the leading therapeutic group worldwide with regards to drug utilisation over the last 15 years.[1]

The most frequently reported adverse effects associated with PPIs include mild gastrointestinal disorders and some reactions affecting the CNS, such as migraine, insomnia, somnolence, vertigo, agitation, depression, confusional states and even hallucinations in seriously ill patients.[2,3] Several cases of endocrine adverse effects, including gynaecomastia putatively induced by PPIs have been published,[4-8] although such reactions are not mentioned for the majority of individual PPIs; indeed, gynaecomastia is only mentioned in the summaries of the product characteristics for omeprazole and its *S*-enantiomer esomeprazole. However, the only formal study that

has addressed the risk of gynaecomastia related to omeprazole use could neither confirm nor discard any significant association.[9] The present study undertook further work to examine a possible association between PPIs and gynaecomastia.

Methods

Information from the Spanish Pharmacovigilance System database was used; this database includes all the adverse drug reaction reports gathered from the Spanish Regional Pharmacovigilance centres between 1982 and 2006; >100 000 reports have been collected. Information collected from decentralised regional centres to which physicians and pharmacists send spontaneous reports of suspected adverse drug reactions, from the pharmaceutical industry, from pharmacovigilance studies and cases published in the literature are also included in the database. Reporting is mandatory by law, although under-reporting is an important flaw of the system. It has been estimated that the overall under-reporting rate is such that only 1 in every 1144 cases of adverse drug reactions are reported (95% CI 928, 1409).[10] Events associated with the use of recently marketed drugs are specifically requested. By definition, cases of overdose are not included in the database. *Ad hoc* committees evaluate all reports and use an algorithm to establish a causal relationship.[11] All reports are included in the database regardless of causality and severity. All reactions are coded according to WHO adverse reaction terminology dictionary.[12]

For the purpose of this study, only spontaneously reported cases of gynaecomastia associated with PPIs that were collected by the Spanish Pharmacovigilance System and that were obtained exclusively from health professionals via the 'yellow card' scheme were analysed.

To study the association of PPIs with gynaecomastia, reporting odds ratios (RORs) and their confidence intervals were calculated;[13,14] additionally, this estimate was also calculated for other anti-ulcer drugs and for spironolactone – the latter as a positive control. The ROR is a disproportionality measure based on a 2×2 contingency table, which is calculated by dividing the odds of exposure (quotient of number of exposed by the number of non-exposed) in cases by the odds of exposure in non-cases.[15] In so doing, all reported events of the outcome of interest in the database, i.e. gynaecomastia, were defined as cases and the rest of events in men as controls.

Results

Twenty-four cases of gynaecomastia in patients receiving PPIs have been retrieved for the period from January 1982 to July 2006; the main features of the patients are shown in table I. The median age of the cases in this series was 65.5 years (range 26–90 years). The median time to onset for the reaction was 91 days, ranging from 8 days to 4.8 years; eight patients developed gynaecomastia within 2 months of treatment initiation and 14 did so after 2 months. The time to onset was unknown for two patients. Fourteen patients who developed gynaecomastia during PPI treatment were receiving other drugs at the same time. There was a temporal relationship between gynaecomastia and PPI treatment in all cases. In most of the cases, gynaecomastia improved after PPI withdrawal (11 of 15 cases in which this information was known); the median recovery period was 76 days (range 18–303 days); in five of six patients in whom the medication was not withdrawn and the outcome was known, the condition continued. For ten patients, no other drugs or conditions known to be related to gynaecomastia were reported.

The ROR values showing the association between gynaecomastia and other anti-ulcer drugs or spironolactone are presented in table II.

Discussion

The data presented in this study strongly suggest an association between gynaecomastia and the use of PPIs. Although a causal relationship has not been, and cannot be, established on a case report basis, some of the features of the present series point to such a possibility. For all patients there was a clear temporal sequence between the administration of PPIs and the onset of the condition; in most of them, gynaecomastia resolved or improved after drug

Table I. Proton pump inhibitor-induced gynaecomastia: main features of a series collected by the Spanish Pharmacovigilance System 1982–2006

Case no.	Age (years)	Drug (dosage in mg/day)	Action	Time to onset[a] (days)	Outcome (duration in days)	Other drugs/comments
1	80	Lansoprazole (30)	Withdrawn	33	Resolved (32)	Dipotassium clorazepate, nitrendipine
2	60	Lansoprazole (30)	Continued	4.8 years	Did not resolve	
3	58	Omeprazole (20)	Withdrawn		Resolved (41)	Treated with lansoprazole after omeprazole discontinuation
4	49	Omeprazole (20)	Withdrawn	66	Resolved (85)	Amlodipine, aspirin (acetylsalicylic acid)
5	73	Omeprazole (20)	Withdrawn	95	Did not resolve	Allopurinol, calcium carbonate, doxazosin, calcitriol
6	90	Omeprazole (20)	Continued	2.5 years	Did not resolve	Spironolactone, altizide (althiazide), lormetazepam, nitroglycerin, atenolol, lactulose, aspirin
7	63	Omeprazole (20)	Continued	183	Did not resolve	Itraconazole, ciclosporin, furosemide, azathioprine, prednisone
8[b]	36	Omeprazole (20)	Withdrawn	36	Resolved (102)	
9	74	Lansoprazole (15)	Continued	32	Resolved (23)	Omeprazole (20), cisapride, diltiazem
10	77	Omeprazole (20)	Withdrawn	91	Resolved (76)	Nifedipine
11	47	Omeprazole (20)	Withdrawn	8	Resolved (18)	Clarithromycin, lysine acetylsalicylate, prednisone
12	67	Omeprazole (20)	Withdrawn	361	Resolved (303)	Diltiazem (120), pravastatin, lorazepam, triflusal, nitroglycerin
13	70	Omeprazole (20)	NS	61	NS	
14	30	Omeprazole	Withdrawn	15	Did not resolve	
15	59	Omeprazole	Withdrawn	20	Did not resolve	Almagate
16	64	Omeprazole (20)	Withdrawn	276		Cisapride
17	68	Omeprazole (20)	Withdrawn	4 years	Resolved (90)	Surgery needed
18	73	Omeprazole (20)	Withdrawn	NS	Did not resolve	Tamsulosin
19	47	Omeprazole (20)	Continued	2 years	Did not resolve	
20	26	Omeprazole (20)	Withdrawn	277	NS	
21	76	Omeprazole (NS)	Continued	365	Did not resolve	Allopurinol, cyproterone, leuprorelin (leuprolide). Patient had neoplasia
22	54	Omeprazole (20)	Withdrawn	91	Resolved (26)	Venlafaxine, atorvastatin, clorazepate, dipyrone (metamizol), zolpidem, trazodone
23	71	Omeprazole (20)	Withdrawn	58	Resolved (91)	
24	90	Rabeprazole (20)	Withdrawn	32	Resolved (134)	Unilateral gynaecomastia

a The time between the start of treatment and clinical diagnosis of gynaecomastia as recorded on the yellow card.

b The details of case number 8 have previously been published.[6]

NS = not stated.

Table II. Disproportionality estimates for proton pump inhibitors and other anti-ulcer drugs in the Spanish Pharmacovigilance System database 1982–2006

Drug	Cases of gynaecomastia[a]		RORs (95% CI)	
	exposed	non-exposed	crude	adjusted by age
Cimetidine	8/54	303/35 867	20.41 (9.55, 43.62)	27.76 (11.81, 65.25)
Ranitidine	9/347	302/35 574	3.11 (1.59, 6.09)	3.74 (1.73, 8.06)
Omeprazole	21/503	290/35 418	5.28 (3.36, 8.29)	5.23 (3.32, 8.26)
Lansoprazole[b]	3/77	308/35 844	0.97 (0.14, 6.82)	
Rabeprazole[b]	1/14	310/35 907	8.83 (1.15, 67.73)	
Spironolactone[c]	78/196	233/35 725	100.69 (73.58, 137.79)	89.30 (63.96, 124.67)

a Interpreted as cases of gynaecomastia in exposed and in non-exposed individuals, respectively; all reports in individuals receiving the drugs of interest are considered exposed, reports in individuals who were not receiving these drugs are considered non-exposed.

b The age-adjusted ROR was unable to be calculated due to the small number of cases.

c Considered as a positive control for gynaecomastia.

RORs = reporting odds ratios.

withdrawal. Notwithstanding, in a few cases some other drugs might have contributed partially or totally to the condition. No clear characteristics could be identified in patients who developed gynaecomastia; spontaneous reports often do not contain clinical information. The elapsed time between initial drug exposure and the development of gynaecomastia is consistent with the pathogenesis of this reaction.

Disproportionality measures, such as RORs, express to what extent the number of observed cases differs from the number of expected cases; they represent a step forward in signal detection in pharmacovigilance, as they allow they use of a quantitative approach in addition to the usual qualitative analysis.[16] The ROR for omeprazole and gynaecomastia in our study is statistically significant, but the ROR for the other PPIs fails to reach significance when adjusted for age, possibly due to the small numbers involved.

Similarly, data from the literature seem to reinforce this association since two additional case series have previously been published.[7,8] In the first one, the WHO Collaborating Centre for International Drug Monitoring identified 13 cases of omeprazole-induced gynaecomastia plus 12 of impotence; in the second one, the Australian Adverse Drug Reactions Advisory Committee identified ten new cases of gynaecomastia related to omeprazole – in eight cases no other suspicious drug was present. The only formal study that has addressed the risk of gynaecomastia related to omeprazole could neither confirm nor discard any significant association.[9] Since the most common duration of issued prescriptions for patients included in that study was <60 days (87% of all prescriptions) – the mode being 30 days – and the time to onset for this reaction is generally longer, not many *a priori* cases would be expected to appear (median time to onset in the present series was 91 days and in the series by Lindquist and Edwards[7] the mean time to onset was 88 days). In fact, only one case of gynaecomastia was found among 9972 treated patients,[9] which accounted for an incidence rate far below the basal incidence of gynaecomastia[17,18] and yielded a non-significant relative risk of 0.6 (95% CI 0.1, 3.3).

Gynaecomastia may be the result of an upward imbalance in the estrogen/androgen ratio due to an inhibition of estradiol metabolism by omeprazole, thereby leading to an increase in estradiol, which in turn serves as a common trigger for the induction of gynaecomastia. In fact, omeprazole at high concentrations has been observed to inhibit cytochrome P450 (CYP)3A4 – which strongly catalyses the oxidation of estradiol, its major catabolic pathway – giving rise to an increase in estradiol levels.[19] Since omeprazole is extensively metabolised by CYP2C19, for which >15 variant alleles associated with a decreased metabolism have been identified[20] – the frequency of poor metabolisers among Europeans ranges from 1% to 6%[21,22] – it is possible that

such patients, when treated for long periods with higher doses of omeprazole, would be at particular risk for the development of gynaecomastia. For antihistamines like cimetidine, a similar mechanism is mediated by CYP3A4, in combination with an androgenic receptor blockage, has been proposed;[23,24] however, spironolactone promotes gynaecomastia through the inhibition of 17-β hydroxysteroid dehydrogenase.[19]

Conclusion

In summary, this series further emphasises the possible association between PPIs and endocrine effects such as gynaecomastia; this condition is more than a cosmetic embarrassment as it is often painful. Doctors should be aware of this potential adverse reaction that, considering the wide use of this medication, could affect a large number of patients; besides, the recognition of drug-induced gynaecomastia is important to prevent unnecessary sophisticated investigations for underlying systemic or endocrine diseases.

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