Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Proton-pump inhibitors and gynecomastia

Introduction

Proton-pump inhibitors are widely used in the treatment of duodenal and gastric ulcers, reflux-oesophagitis, dyspepsia, the Zollinger-Ellinger syndrome, in combination with antibiotics for the treatment of Helicobacter pylori infections and in the prevention of gastric complications in susceptible patients, who use non steroidal anti-inflammatory drugs.
Proton pump inhibitors suppress the gastric acid secretion by binding to the proton pump of the parietal cell.
Common adverse drug reactions of proton-pump inhibitors include: nausea, vomiting, abdominal pain, constipation, diarrhea, flatulence, headache and dizziness. Gynecomastia is an ADR which is mentioned in the SPC of Losec® (omeprazole) and Nexium® (esomeprazole), but not in the SPCs of the other proton-pump inhibitors[1-6].
Gynecomastia is defined as growth of the male mammary tissue, unilateral or bilateral. It commonly occurs in puberty and old age. Gynecomastia is most often benign and reversible.
The most common cause of gynecomastia is an imbalance between oestrogens and androgens. Several drugs can induce a decreased testosterone level [7,8].

Reports

On June 27, 2005 the database of the Netherlands Pharmacovigilance Centre contained 28 reports concerning gynecomastia associated with the use of proton- pump inhibitors. In most reported cases the latency period was several weeks to months after start. By definition all cases concerned men.
Furthermore Lareb received several reports of decreased libido, erectile dysfunction and impotence, problems which also might be related tot a decrease in testosterone levels.

Table 1. reports of gynecomastia associated with the use of proton-pump inhibitors

Patients age*	Suspected drug(s), dose	Concomitant medication	Suspected adverse drug reaction(s)	Time to onset	Remarks
A, 70	omeprazole, 1x40mg	maprotiline, lactulose	gynecomastia unilateral	2 months	
B, 61	omeprazole, 1x40mg	distigmine acetylcysteine, carbasalate calcium	gynecomastia	8 weeks	
C, 62	omeprazole 2x20mg	not reported	gynecomastia unilateral	7 weeks	
D, 46	omeprazole, 1x20mg	not reported	gynecomastia unilateral	12 months	
E, 38	omeprazole, 1x10mg	chloormezanon, tramadole	gynecomastia unilateral	months after strart	medication was already withdrawn
F, 50	omeprazole, 1x40mg	not reported	gynecomastia	2 month safter start	2 weeks after withdrawal
G, 54	omeprazole, 1x20mg	pancrease, acetylcysteine, ciprofloxacine	gynecomastia unilateral	unknown	
H, 72	omeprazole, 1x20mg	maprotiline, lactulose	gynecomastia	2 months	
I, 61	pantoprazole, 1x40mg	simvastatin	gynecomastia		omeprazole has been used previously
J, 66	omeprazole, 1x20mg	enalapril, atenolol,	gynecomastia bilateral	1 month	

Patients age*	Suspected drug(s), dose	Concomitant medication	Suspected adverse drug reaction(s)	Time to onset	Remarks
K, 47	omeprazole, 1x20mg, spironolacton, 1x100mg	norfloxacine, furosemide	gynecomastia bilateral; rash; arthralgia	not reported	
L, 31	lansoprazol, 30mg	not used	gynecomastia bilateral	4 days	recovered after withdrawal
M, 50	omeprazole, 2x20mg	not reported	gynecomastia	unknown	
N, 70	omeprazole, 1x10mg	not reported	gynecomastia, pruritus,flatulence, alopecia, depressed state	unknown	
O, 46	pantoprazole, 1x 40mg	not reported	gynecomastia	unknown	
P, 47	pantoprazole, 1x20mg propranolol, 1x80mg	efavirenz	gynecomastia	3 months	
Q, 75	omeprazole, 1x20mg, pantoprazole, 1x 40mg	lorazepam, paracetamol, alfacalcidol, diclofenac, ferrogluconate, sotalol, epoitine	gynecomastia	6 months	
R, 52	omeprazole, 1x40mg	rofecoxib, levocabastine	gynecomastia, weight increase	4 weeks	
S, 39	omeprazole, ?	not reported	gynecomastia	unknown	
T, 46	paroxetine, 20mg, ranitidine, 300mg, pantoprazole, 40mg	oxazepam	gynecomastia	unknown	
U, 64	pantoprazole, 1x20mg	ipratropium, salbutamol, fluticason, hydrochlorothiazide, atorvastatine, celiprolol, insulin	painfull gynecomastia	2 year	
V, 42	esomeprazole 1x40mg	not reported	gynecomastia	days after start	
W, 51	omeprazole, 1x40mg	not reported	gynecomastia unilateral	unknown	
X, 71	omeprazole, 1x20mg	simvastatine, carbasalate calcium, propranolol, bromazepam	gynecomastia	2,5 year	
Y, 56	esomeprazole 1x40mg	hydrochlorothiazide, alendronate	gynecomastia	unknown	
Z, 87	pantoprazole, 1x20mg	pravastatine, diazepam	gynecomastia	3 months	
AA, 64	rabeprazole, 1x80mg	**acetylsalicylic acid, bumetanide, celiprolol, losartan, pravastatine, diclofenac, allopurinol, temazepam, tiotropium	gynecomastia	unknown	breast tissue was surgically removed
AB, 88	spironolacton, 1x25mg, pantoprazol, 1x40mg	furosemide, digoxine, isosorbidemononitrate,	gynecomastia bilateral	5 months	

* By definition all patients are male
** In this report all drugs were mentioned as suspect

Other sources of information

Literature
A literature search reveals incidental case reports of gynecomastia associated with the use of omeprazole and lansoprazole [9]. However in a case control study with a cohort of 80,000 men, the association between gynecomastia and the use of omeprazole could not be confirmed [10].

Databases
The association of gynecomastia and the proton-pump inhibitors is disproportionally present in the WHO database with lansoprazole, omeprazole, pantoprazole and rabeprazole (table 2).

Table 2. Overview of the WHO database of reports of gynecomastia associated with the use of proton-pump inhibitors

Drug	gynecomastia and drug	drug total	ROR (95%CI)
esomeprazole	8	1745	1.82 (0.91-3.65)
lansoprazole	40	6126	2.61 (1.91-3.56)
omeprazole	217	20032	4.42 (3.86-5.07)
pantoprazole	15	2701	2.16 (1.30-3.58)
rabeprazole	12	1883	2.48 (1.40-4.37)

It was not possible to calculate the ROR for all proton-pump inhibitors in the Lareb database, the associations of omeprazole and pantoprazole and gynecomastia are disproportionally present (table 3)

Table 3. overview of the Lareb database of reports of gynecomastia associated with the use of proton-pump inhibitors

Drug	gynecomastia and drug	drug total	ROR (95%CI)
omeprazole	17	735	8.5 (5.08-14.1)
pantoprazole	8	210	13.4 (6.50-27.7)

Mechanism
A possible mechanism of gynecomastia induced by proton-pump inhibitors is yet unknown. A case report published by Rosenshein and Flockhart might give an explanation. This case concerns a 42-year-old female with libido loss and a decreased testosterone level, which is related to the intake of esomeprazole. In this article the authors postulate that esomeprazole causes induction of Cyp3A4 resulting in a increased testosterone metabolism [11].

Conclusion
Lareb received 28 reports of gynecomastia in association with proton-pump inhibitors, most of these cases concerned omeprazole. In the WHO data the association gynecomastia with other the proton-pump inhibitors is also disproportional suggesting gynecomastia might be a class effect of the proton- pump inhibitors.

References

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