

## Effect of omeprazole on reproductive hormonal levels and sexual function in male patients with peptic ulcer disease

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### الخلاصة

لتقييم تأثير الامبرازول بجرعه ثابتة على الوظيفة الجنسيه (باستخدام استبيان الابلاغ الذاتي) ومستوى الهرمونات التناسلية في مصل الدم مثل هرمون الشحمون الخصوي، هرمون الحليب، هرمون المحفز للجريبي، هرمون اللوتين وهرمون استرادايول عند الذكور المشخصين حديثاً بداء القرحة الهضمية بالمقارنة مع مجموعة الضبط.

تم استقبال المرضى ومقابلتهم في العيادة الخارجيه- القسم الطبي لمستشفى ابن سينا التعليمي. تم انتقاء المرضى وفق معايير خاصه. من اصل 60 مريضاً تم انتقاءهم فقط 43 اكملوا دراسة المتابعه. في البدايه تم تقييم الوظيفة الجنسيه باستخدام استبيان الابلاغ الذاتي وتم سحب عينات دم وتحديد مستوى الهرمونات التاليه، هرمون الشحمون الخصوي، هرمون الحليب، الهرمون المحفز للجريبي، هرمون اللوتين وهرمون استرادايول في مصل الدم باستخدام تقنية enzyme-linked fluorescent assay بواسطة جهاز VIDAS. بعدها تم وضع المرضى على علاج الامبرازول بجرعة 20 ملغم مرتين يومياً لمدة 45 يوماً مع الكلارثرومايسين بجرعة 500 ملغم مرتين يومياً والميترونيدازول بجرعة 500 ملغم مرتين يومياً مدة العشرة ايام الاولييه من العلاج.

في نهاية الفتره المقترحه لدراسة المتابعه تم اعاده تقييم الوظيفة الجنسيه للمرضى وتم سحب عينات دم وتحديد مستوى هرمون الشحمون الخصوي، هرمون الحليب، الهرمون المحفز للجريبي، هرمون اللوتين وهرمون استرادايول في مصل الدم باستخدام نفس التقنيه التحليليه. ادخل لهذه الدراسة ايضاً اربعون من الذكور الاصحاء من اعمار مقاربه لمجموعة المرضى كمجموعة ضبط. تم سحب عينات دم منهم وقياس مستوى نفس الهرمونات المذكورة اعلاه مع تحديد الوظيفة الجنسيه باستخدام نفس استبيان الابلاغ الذاتي. تبين ان هناك اختلافات غير معنوية في مفردات الوظيفة الجنسيه ومستويات هرمون الشحمون الخصوي، هرمون الحليب، الهرمون المحفز للجريبي، هرمون اللوتين وهرمون استرادايول في مصل الدم لدى المرضى في مرحلة قبل العلاج بالمقارنة مع مجموعة الضبط. بعد العلاج كان هنالك انخفاضاً معنوياً في مستوى هرمون الشحمون الخصوي بالمقارنة مع فترة قبل العلاج ومجموعة الضبط، مع اختلافات غير معنويه في مفردات الوظيفة الجنسيه ومستوى هرمون الحليب، الهرمون المحفز للجريبي، هرمون اللوتين وهرمون استرادايول في مصل الدم.

استنتج ان العلاج الطويل بعقار الامبرازول قد يسبب انخفاضاً في مستوى هرمون الشحمون الخصوي مع تأثيرات غير معنويه على مستوى هرمون الحليب، الهرمون المحفز للجريبي، هرمون اللوتين وهرمون استرادايول في مصل الدم لدى المرضى الذكور المشخصين حديثاً بداء القرحة الهضمية.

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**Abstract**

**Objectives:** To assess the effects of Omeprazole at a fixed dose on sexual function (by self reporting questionnaire) and serum levels of testosterone, prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E<sub>2</sub>) in newly diagnosed male patients with peptic ulcer disease, in comparison to healthy controls.

**Patients and Methods:** Patients were received and interviewed in Ibn-Sina Hospital, out-patient clinic, medical section and were selected according to certain criteria. From 60 male patients selected only 43 completed the follow-up study. Initially sexual function were assessed using a self-reporting questionnaire and a blood samples were taken with assay of serum testosterone, prolactin, FSH, LH and E<sub>2</sub> using Minividus technique. Patients than put on Omeprazole therapy 20mg twice daily for 45 days with Clarithromycin 500mg twice daily and Metronidazole 500mg twice daily for the initial 10 days. By the end of the suggested period of follow-up, sexual function were assessed by self-reporting questionnaire and other blood samples were taken with assay of serum testosterone, prolactin, FSH, LH and E<sub>2</sub> using the same analytical technique. Included in this study also forty apparently healthy age, matched male volunteers as a control group . Blood samples were also withdrawn from them and assay of serum testosterone prolactin, FSH, LH and E<sub>2</sub> were done , with assessment of sexual function using the same self reporting questionnaire. For both groups ( the patients and controls), body mass index were calculated using special equation.

**Results:** There was insignificant differences in the parameters of sexual function between patients with peptic ulcer disease in the pre-therapy stages and the controls, so as in the serum levels of testosterone, prolactin, FSH, LH and E<sub>2</sub>. After therapy there was a significant differences in the mean serum level of testosterone from the pre-therapy stage and the controls, with insignificant differences in the sexual function parameters and serum levels of prolactin, FSH, LH and E<sub>2</sub>.

**Conclusion:** Long term Omeprazole therapy might cause a reduction in the level of testosterone hormone with insignificant effects on other sexual hormonal levels (prolactin, FSH, LH and E<sub>2</sub>) within significant effect on sexual function, in male patients with peptic ulcer disease.

**Key words:** Peptic ulcer, Male patients, Omeprazole, Reproductive hormonal levels.

## Introduction

Omeprazole, belongs to the class of proton pump inhibitors. The active ingredient in its delayed release capsules, is a substituted benzimidazole, 5-methoxy-2-[[[4-methoxy-3,5 dimethyl-2-pyridinyl ) methyl]-1H-benzimidazole. It is registered for use in benign peptic ulcers, reflux esophagitis, acid-related dyspepsia and Zollinger, Ellison syndrome<sup>(1)</sup>. It is structurally related to rabeprazole, Lansoprazole and pantoprazole<sup>(2)</sup>. These are prodrugs chemically transformed within the acidic secretory canaliculi of the parietal cell into a cyclic sulphenamide which then reacts with luminal thiol groups of the H<sup>+</sup>/ K<sup>+</sup>-ATPase to form a disulphide inhibitor complex<sup>(3)</sup>. Many drugs used in therapy of peptic ulcer disease have been implicated in causing adverse hormonal disturbances including licorice and cimetidine<sup>(4,5)</sup>. The aims of this study were to assess the sexual function (by a self-reporting questionnaire) and serum levels of testosterone, prolactin, FSH, LH and E<sub>2</sub> in newly diagnosed male patients with peptic ulcer disease after an omeprazole therapy at a fixed dose for 45 days in comparison to healthy controls.

## Patients and Methods

This study was conducted in the outpatient clinic in Ibn-Sina Hospital, from Sept. 2010 to March 2011. Patients were selected according to certain criteria, including, male married patients, newly diagnosed with peptic ulcer disease (proved by endoscopy) non-smoker, with no cardiovascular, hepatic, renal, neurological or endocrinal disease, on no drug therapy. Out of 60 patients selected only 43 completed the study. Their mean  $\pm$  SD ages  $27.20 \pm 5.98$  years (ranged between 18 and 47 years). Initially sexual function were assessed using a self reporting questionnaire<sup>(6)</sup>, parameter assessed include, loss of interest in sex, problems with erection; problems with ejaculation's and number of intercourse / 2 weeks. A blood samples were taken and assay of serum testosterone, prolactin, FSH, LH and E<sub>2</sub> using commercial kits and minividus technique, patients then put on Omeprazole capsule

(Gasec, Mepha-Switzerland) 20 mg twice daily for 45 days (with Clarithromycin 500mg and mentronidazole 500 both twice/day for the initial 10 days). After the suggested period of study, patients were interviewed and assessment of sexual function were done, using the same self-reporting questionnaire and another blood samples were taken with assay of the same parameters mentioned above, using the same analytical technique. Included in this study also, forty apparently healthy, Non-smoker males taken as a control. Their mean  $\pm$  SD age  $26.92 \pm 6.12$  years (ranged between 18 and 45 years). Sexual function were assessed using the same self-reporting questionnaire and a blood samples, were taken with assay of the same biochemical parameters mentioned above.

For both the patients and controls, body mass index (BMI) were calculated using the following equation:

$$\text{BMI} = \text{Weight (Kg)} / \text{height (m}^2\text{)}^{(7)}$$

Table 1 shows the characteristics of patients and controls.

### Statistical analysis

Standard statistical methods to determine the mean and standard deviation (SD). Unpaired t-test was used to compare results for the measured parameters between controls and patients in the pre and post-therapy stages. Paired t-test and z-test were used to compare results for the measured parameters between patients in the pre and post-therapy stages.

Differences between observations were considered significant at  $P \leq 0.005$  (Kirkwood 1988)<sup>(8)</sup>

### Results

The characteristic of subjects in this study( patients and controls) are given in table 1.

#### a- Sexual function:

There was insignificant differences in the parameters evaluating sexual function between patients in the pre-therapy stage (mean  $\pm$  SD number of sexual intercourse  $3.27 \pm 1.16$ ); post-therapy stage (mean  $\pm$

SD number of sexual intercourse  $3.23 \pm 1.13$ ) and the controls (mean  $\pm$  SD number of sexual intercourse  $3.37 \pm 1.11$ ).

Out of 43 patients only one case (2.32%) developed problems with erection after omeprazole therapy.(Table 2)

b- Serum hormonal levels.

I. Comparison with controls.

There was insignificant differences in the mean serum levels of testosterone, prolactin, FSH , LH and E<sub>2</sub> between patients in the pre-therapy stages and the controls (table 3).

There was a significant differences in the mean serum level of testosterone between patients in the post therapy stage and the controls with insignificant differences in the mean serum levels of Prolactin, FSH, LH and E<sub>2</sub> (Table 4).

II. Comparison between patients at pre and post-therapy stages.

There was insignificant differences ( $P < 0.0001$ ) in the mean serum level of testosterone between patients in the pre and post-therapy stages with insignificant differences in the mean serum level of prolactin, FSH, LH and E<sub>2</sub> (Table 5).

## Discussion

Many drugs have been implicated in causing an adverse endocrinal effects. The effect of the medication on the male reproductive endocrine balance are usually discussed in terms of their effects on testosterone metabolism<sup>(9,10)</sup>.

This study reveals insignificant effect of omeprazole therapy at fixed dose for 45 days on parameters of sexual function, with significant reduction in serum levels of testosterone in comparison to pre-therapy stage and controls.

It has been reported in the rat that a high dose of lansoprazole 150 mg/Kg/d orally decreased the blood level of testosterone and produced an associated increase in luteotrophic hormone<sup>(11)</sup>.

Rosenshein *et al* (2004), reported a 42 years old women with previously normal sexual function, who gradually developed loss of libido during treatment with esomeprazole which was improved by adding oral testosterone supplementation and deteriorated after testosterone withdrawal. There was steady improvement of both sexual

function and serum free testosterone concentration after discontinuation of esomeprazole<sup>(12)</sup>.

Coulson *et al* (2003). Concluded from their study in male Sprague- Dawley rats, that lansoprazole treatment for 14 days induced hepatic CYP-dependent testosterone metabolism in vitro and enhanced plasma clearance of radiolabelled testosterone in viro and that these effects might contribute to depletion of circulating testosterone levels<sup>(11)</sup>.

Dowie *et al* (1988) , have demonstrated in vivo that omeprazole blocks an early step in steroidogenesis; this has been confirmed in vitro, indicating weak inhibition of cholesterol side-chain cleavage activity<sup>(13)</sup>.

Lindquist and Edwards gives 15 reports of impotence and 15 reports of gynaecomastia associated with the use of omeprazole therapy<sup>(14)</sup>. Also Carvajal et al (1992) reported 3 patients who developed impotence with unilateral gynaecomastia in relation to omeprazole therapy<sup>(15)</sup>.

Our results might be explained by the results of Dowie et al<sup>(13)</sup> and the structural similarity of omeprazole to lansoprazole which causes the depletion of circulating testosterone as reported by Coulson *et al*<sup>(11)</sup>.

To the best of our knowledge this might be the first follow-up study in newly diagnosed male patients with peptic ulcer disease, put on omeprazole at fixed doses for 45 days, in which assessment of sexual functions and assay of serum levels of testosterone, prolactin, FSH, LH and E<sub>2</sub> were done in comparison to healthy controls.

In conclusion

This study might indicate significant effect of omeprazole therapy, in newly diagnosed male patients with peptic ulcer disease, on serum testosterone level with insignificant effects on prolactin, FSH, LH and E<sub>2</sub>.

**Table 1. The characteristics of newly diagnosed patients with peptic ulcer disease and the controls.**

Parameters (Mean ± SD)	Patients	Controls	P-value
Number	43	40	NS
age (years)	26.92 ± 6.12	27.20 ± 5.98	NS
BMI	22.19 ± 2.02	22.85 ± 2.00	NS

NS: Non-significant differences at p≤0.05

**Table 2. Parameters of sexual function in male patients with peptic ulcer before and after therapy.**

Parameters	Result	Before		After		p-value
		No.	%	No.	%	
In interest in sex	+ve	0	0.0	0	0.0	(NS)
	-ve	43	100	43	100	
Problem with erection	+ve	0	0.0	1	2.3	(NS)
	-ve	43	100	42	97.7	
Problem with ejaculation	+ve	0	0.0	0	0.0	(NS)
	-ve	43	100	43	100	
Number of intercourse / 2 weeks	Mean $\pm$ SD					(NS)
	Before		After			
	3.27 $\pm$ 1.16		3.23 $\pm$ 1.13			

NS = Not significant using paired Z-test

**Table 3. Comparison of controls and newly diagnosed patients with peptic ulcer disease in the pre-therapy stage with regard serum level of testosterone prolactin, FSH, LH, and E2.**

parameters	Mean $\pm$ SD		P-value
	controls	Pre-therapy patients	
Testosterone (ng/ml)	5.61 $\pm$ 1.25	5.31 $\pm$ 1.76	NS
Prolactin (ng/ml)	10.97 $\pm$ 2.57	12.14 $\pm$ 7.00	NS
FSH (mIU/ml)	3.69 $\pm$ 0.93	4.15 $\pm$ 2.70	NS
LH (mIU/ml)	3.52 $\pm$ 1.93	3.42 $\pm$ 2.23	NS
E2 (pg/ml)	27.30 $\pm$ 6.19	29.96 $\pm$ 7.70	NS

Comparison by Unpaired t-test

NS: Non-significant differences

**Table 4. Comparison of controls and newly diagnosed patients with peptic ulcer disease in the post-therapy stage with regard serum level of testosterone prolactin, FSH, LH, and E2.**

parameters	Mean $\pm$ SD		P-value
	controls	Post-therapy patients	
Testosterone (ng/ml)	5.61 $\pm$ 1.25	3.87 $\pm$ 1.72	S
Prolactin (ng/ml)	10.97 $\pm$ 2.57	12.12 $\pm$ 7.10	NS
FSH (mIU/ml)	3.69 $\pm$ 0.93	4.14 $\pm$ 2.71	NS
LH (mIU/ml)	3.52 $\pm$ 1.93	3.40 $\pm$ 2.24	NS
E2 (pg/ml)	27.30 $\pm$ 6.19	30.10 $\pm$ 7.72	NS

Comparison by Unpaired t-test, NS: Non-significant differences

,S: Significant differences at  $p \leq 0.05$ .

**Table 5. Comparison of patients with peptic ulcer disease in the pre and post therapy stages with regard measured parameters.**

parameters	Mean ± SD		P-value
	Pre-therapy patients	Post-therapy patients	
Testosterone (ng/ml)	5.31 ± 1.76	3.87± 1.72	S
Prolactin (ng/ml)	12.14 ± 7.00	12.12 ± 7.10	NS
FSH (mIU/ml)	4.15 ± 2.70	4.14 ± 2.71	NS
LH (mIU/ml)	3.42 ± 2.23	3.40 ± 2.24	NS
E2 (pg/ml)	29.96 ± 7.70	30.10 ± 7.72	NS

Comparison by Paired t-test

NS: Non-significant differences

S: Significant differences at  $p \leq 0.05$

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