

## Relationship between atenolol and early development of heart failure in hypertensive patients

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### الخلاصة

هو واحد من مجموعة الأدوية التي تعمل على غلق مستقبلات بيتا، وهو شائع وواسع الاستعمال في معالجة ارتفاع ضغط الدم، اذ يعمل على خفض ضغط الدم المرتفع بشكل فعال ولكن له العديد من التأثيرات الجانبية على مختلف أنسجة وأعضاء الجسم، البعض منها قد تكون خطيرة.

### الهدف

لإثبات وجود علاقة بين عقار التينورمين وحدث عجز القلب المبكر وذلك من خلال دراسة تأثير هذا العقار على مستويات بعض المكونات الموجودة في مصل الدم منها: مستويات الكوليسترول الكلي في المصل و مستويات الكلسيريديتات الثلاثية و مستوى و فعالية الإنزيم الناقل (اسبارتيت ترانس امينيز)، ومقارنة النتائج لمجموعة مرضى ارتفاع ضغط الدم الذين يستعملون هذا العقار لفترة قصيرة ومجموعة أخرى يستعملونه منذ فترة طويلة. لقد تم اختيار هذه المكونات بالذات لأنها تعطي فكرة مباشرة عن أمراض الجهاز القلبي الوعائي الممكن حدوثها في المستقبل.

### الطرق

دراسة مقارنة حالات: أجريت الدراسة في مستشفى اليرموك التعليمي لفترة سنة وسبعة أشهر على (40) مريض يعانون من ارتفاع ضغط الدم وتم تقسيم هؤلاء المرضى إلى مجموعتين وفقاً إلى طول فترة استعمالهم لعقار التينورمين:

**المجموعة 1:** و تتألف من (20) مريض، معدل أعمارهم (56±8) سنة واستعملوا التينورمين لفترة زمنية تراوحت بين (1-3) سنوات .

**المجموعة 2:** وتتألف من (20) مريض معدل أعمارهم (55±8) سنة واستعملوا التينورمين لمدة تراوحت بين (4-10) سنوات .

تم أخذ عينات من دم كل مريض لقياس مستويات المكونات المذكورة أعلاه وتمت مقارنة النتائج بين المجموعتين.

## النتائج

كانت معدلات كلٍ من الكوليسترول الكلي و الكلسيريديات الثلاثية والأنزيم الناقل (اسبارتيت ترانس امينيز) في مصول دم المجموعة الثانية مقارنة بالمجموعة الأولى عالية وبمعنوية واضحة  $P < 0.05$ .

## الاستنتاجات

من خلال النتائج التي تم الحصول عليها تبين أن عقار التينورمين يؤدي إلى ارتفاع وزيادة مستويات المكونات المذكورة آنفا وهذه الزيادة تتناسب طردياً مع طول الفترة الزمنية لاستعمال التينورمين وبما أن هذه المكونات تؤثر على الجهاز القلبي الوعائي بمستوياتها العالية وتؤدي إلى حدوث أمراض هذا الجهاز فان التينورمين له علاقة معنوية بحدوث أمراض الجهاز القلبي الوعائي وخصوصاً عجز القلب .

## Abstract

### Background:

Atenolol is one of  $\beta$ -adrenergic receptor blocking agent, that is widely and commonly used in the treatment of hypertension, its lowering high blood pressure effectively but, it has many side effects on different body organs and tissues, some of them are serious.

### Objectives:

To prove the association between Atenolol and heart failure through studying the effects of this drug on the levels of some parameters that are present in the blood including: total serum cholesterol, serum triglyceride and aspartate transaminase enzyme in early and long term usage of this drug by hypertensive patients, these parameters are chosen because they give an early indication about future development of cardiovascular disease.

### Methods:

Case comparative study was conducted in Al-Yarmouk teaching hospital for one year and seven months on (40) hypertensive patients, they were divided into (2) groups according to the duration of the treatment:

Group I: (20) patients with mean age ( $56 \pm 8$ ) years .They used the drug for a period from (1-3) years.

Group II: also (20) patients with mean age ( $55 \pm 8$ ) years used the drug for (4-10) years.

Both groups were with the same number of sex and nearly the same age, venous blood samples are taken from each patients and levels of total serum cholesterol, serum triglyceride (S.TG), and Aspartate transaminase (AST) were estimated and compared between the (2) groups.

### Results:

The mean of total serum cholesterol was significantly higher in group II than in group I ( $p < 0.05$ ) , the mean of S.TG was significantly higher in group II

than in group I ( $p < 0.05$ ), the mean of AST was higher in group II than group I ( $p < 0.05$ ).

### **Conclusion:**

Atenolol causes increase levels of total serum cholesterol, S.TG and AST and this increase is directly proportion to the duration of the drug usage and as they are affect on cardiovascular system and causing cardiovascular diseases by their high levels, so Atenolol has significant correlation with the development of cardiovascular diseases especially heart failure.

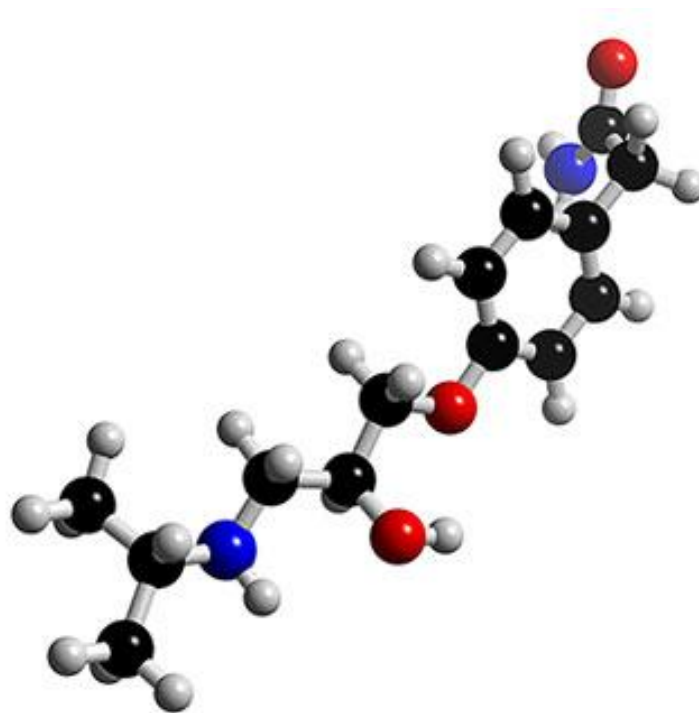
**Key words:** hypertension, Atenolol and side effects, Atenolol antihypertensive, heart failure.

### **Introduction**

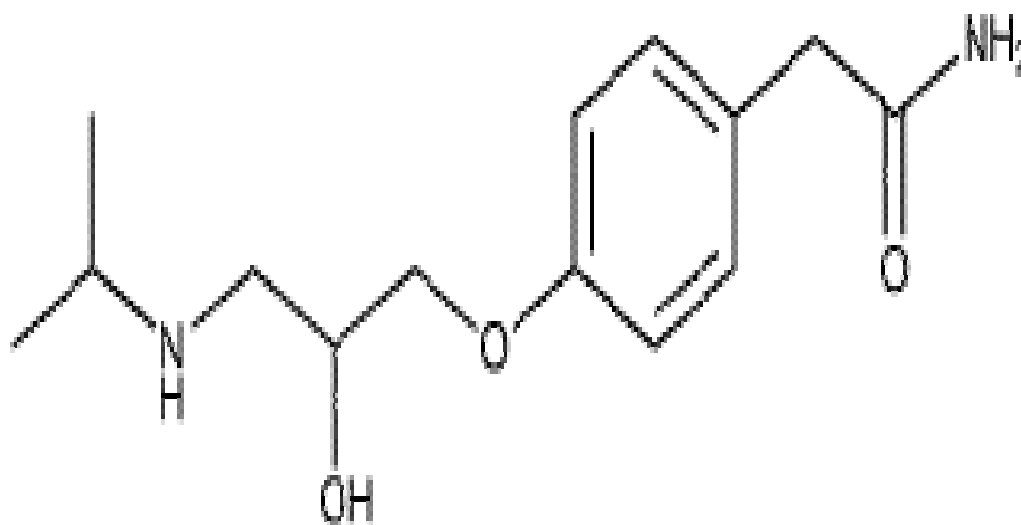
Arterial hypertension is a common health problem representing one of the most frequent diagnoses in the population at large in terms of prevalence and incidence<sup>[1]</sup>. Several studies were carried out to estimate the adult population suffer from arterial hypertension and whom aware of it and are treated with antihypertensive drugs, it was found that antihypertensive drugs consumption has increased from (34.78) daily dose per 1000 inhabitants per day in 1985 to (103.33) daily dose in 1995<sup>[2]</sup>. Among the antihypertensive drugs the group known as  $\beta$ -adrenergic blockers, atenolol is the mostly drug of this group in use, it has therapeutic value in treating cardiovascular symptoms such as: hypertension, angina and arrhythmias<sup>[3]</sup>.

Atenolol is like any other antihypertensive drugs, it lowers both systolic and diastolic blood pressure by its ability to bind to  $\beta$ -adrenergic receptors and prevents their stimulation by catecholamines<sup>[4]</sup>. Atenolol has a selective effect on  $\beta_1$ -adrenergic receptors which are present in the heart and therefore it can be considered cardioselective antihypertensive drug, it can reduce both maximal and submaximal heart rate and delays atriocentric contraction<sup>[5]</sup>. Atenolol is rapidly absorbed from the gut, blood level reach a peak concentration in (2-3) hours due to its hydrophilic nature<sup>[6]</sup>. Metabolism of Atenolol is minimal and almost the total absorbed drug (85-100) % is cleared via excretion in the urine in an unaltered manner<sup>[7]</sup>.

The treatment of hypertension requires long time and continues for years, therefore, the patient are exposed to prolong contact with these drugs, so it would be of interest to evaluate any effects of antihypertensive drugs ( $\beta$ -blockers) among them and for this purpose we choose atenolol because of its wide spread use for the treatment of hypertension, in addition to early development of symptoms of coronary heart disease and heart failure in many patients use this drug that make them either give up using it and or shifting to other antihypertensive drug groups.



Three dimensional structure of Atenolol



The chemical structure of Atenolol is {4-hydroxy-3-[(1-methyl ethyl) amino]propoxy]benzene acetamide} as shown in the figure<sup>[8]</sup>.

### Materials and Methods:

This case comparison study was done in the department of medicine in Al-Yarmouk teaching hospital over a period of one year and seven months from

August 2006 to April 2008 on (40) hypertensive patients (24 females and 16 males) with age ranged from (40-70) year who received atenolol tablets (100)mg as antihypertensive drug for a duration ranged from (1-10)years of treatment for their hypertension, those patients were divided into 2 groups according to the duration of drug use:

**Group I:** consists of (20) patients (12) females and (8) males with mean age ( $56 \pm 8$ ) years, they used Atenolol for a period from (1-3)years.

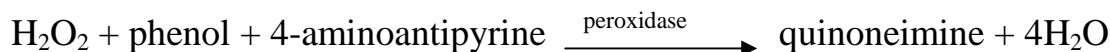
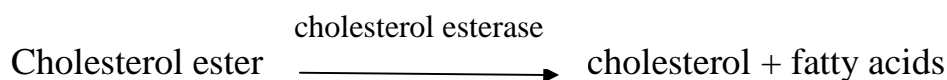
**Group II:** consists of also (20) patients (12) females and (8) males with mean age ( $55 \pm 8$ ) years, the duration of their use for atenolol ranged from (4-10) years.

The patients of both groups were followed continuously, blood samples were obtained for each for measuring and monitoring the levels of: total serum cholesterol, serum triglyceride (S.TG), and serum aspartate transaminase enzyme (AST). The methods of measuring used were:

§ Total serum cholesterol by enzymatic method by using bioMerieux kit<sup>[9]</sup>.

**Principle:**

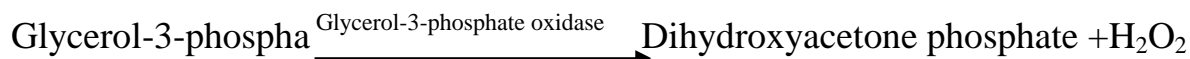
Cholesterol is determined according to the following reactions:



The colour intensity is stable for 30 min. and read at 500 nm.

§ Serum triglyceride by enzymatic method by using GPO kit method<sup>[10]</sup>.

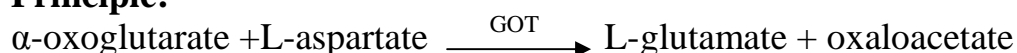
**Principle:**



The colour intensity is stable for 30 min. and read at 500 nm.

§ Serum AST colorimetric method by Reiman-Frankel Kit<sup>[11]</sup>.

**Principle:**



Glutamic- oxaloactic transaminase is measured by monitoring the concentration of oxaloacetate by hydrazone formed with 2,4-dinitrophenylhydrazine.

The colour intensity is stable for 5 min. and read at 530 nm.

The results were obtained and are presented as mean  $\pm$  SD and the data were analyzed by using t-test, the significant level for all tests was taken as P value less than 0.05.

## **Results**

After collection and categorization of data from (40) patients included in the study, statistical analysis was done which revealed the following:

- 1 - There is significant correlation between the levels of total serum Cholesterol for both groups  $P < 0.05$ , with mean for group I ( $239.25 \pm 32.29$ )mg/dl and for group II ( $378.95 \pm 45.27$ ) mg/dl, as shown in table -1-.
- 2 - There is significant correlation between levels of serum triglyceride of both groups  $p < 0.05$  and the mean for group I ( $2.21 \pm 0.38$ )mmol/L and for group II ( $3.91 \pm 0.39$ )mmol/L as shown in table -1-.
- 3 - The levels of serum AST for group I were within the upper limits of normal ranges for this enzyme few of them their blood levels were slightly higher, while group II most of them their blood levels of this enzyme were high. There is significant correlation between the two groups  $P < 0.05$ , mean for group I ( $19.84 \pm 1.22$ ) IU/L and for group II ( $31.57 \pm 4.78$ )IU/L as shown in table-1-.

	n	(Mean $\pm$ SD)mg/d I S.cholesterol	(Mean $\pm$ SD)mmol/ L S.TG	(Mean $\pm$ SD)IU/ L AST
<b>Group I</b>	20	<b>293.25<math>\pm</math>32.29</b>	<b>2.21<math>\pm</math>0.38</b>	<b>19.84<math>\pm</math>1.22</b>
<b>Group II</b>	20	<b>378.95<math>\pm</math>45.27</b>	<b>3.91 <math>\pm</math>0.39</b>	<b>31.57<math>\pm</math>4.78</b>

**P < 0.05**n: number of patients.

**Table1: Mean levels of s.cholesterol, S.TG and AST in group I and group II patients**

## **Discussion**

As it's known that atenolol has an important and rapid effect in lowering both systolic and diastolic blood pressure which can not be denied and, therefore, its widely used all over the world for the treatment of hypertension its an efficient antihypertensive but on the other hand it has many side effects ,despite there is no drug free of side effects ,sometimes they might be serious

,among the serious side effects of atenolol is the development of heart failure inspite of its use for reducing cardiovascular morbidity and mortality<sup>[12]</sup>.

In this study, we tried to shed a light about the relationship between atenolol and heart failure through studying the effects of atenolol on some constituents that are present in the blood which give an indication about future development of cardiovascular problems in the patients using this drug.

From the results obtained it was noticed the high levels of the constituents mentioned above in group II in comparison to group I , that is because group II exposed to the effects of atenolol for long period of time than in group I, it was proved by some studies done in USA that atenolol can lead to increase plasma triglyceride and total cholesterol as well as high density lipoprotein cholesterol value<sup>[13,14]</sup>.During post marketing experience with atenolol the following have been reported in relationship to the use of the drug: elevated liver enzymes and /or bilirubin, development of antinuclear antibodies and lupus syndrome<sup>[15]</sup>. The predominant syndrome following atenolol use are: lethargy, sinus pause, bradycardia and congestive heart failure<sup>[16]</sup>.

The mechanism by which atenolol causing these changes which are leading finally to the development of heart failure is not yet known but its thought that its due to its effect on cardiac muscle directly which cause reduces of myocardial contractility, heart rate, cardiac out put, it causes decrease in peripheral blood flow and central effect by decrease sympathetic out flow and suppression of rennin activity, these all cause decrease in nutrients, oxygen and finally the energy required by the body organs and tissues, here the indirect effect of atenolol will start which cause liver to increase its activity as a compensatory mechanism, this is done by increasing, gluconeogenesis, glycogenolysis, glycolysis and so on in order to supply the required energy and nutrients to meet the body needs for its normal functions, these all lead to increase levels of AST, serum cholesterol and serum triglyceride, these changes are remain as long as the exposure to atenolol is continues until the fatigue of the liver and the changes become irreversible with the prolong use of this drug leading finally to the development of heart failure, on the other hand the cardiac muscle will become fatigue with prolong exposure to atenolol due to its mechanism on this muscle causing it unable to contract efficiently and ending with failure<sup>[17]</sup>. This can explain the results that have been obtained in this study. Finally and in conclusion this study proved an evidence that prolong use of atenolol leading to the development of heart failure.

For that all we recommend that apart from those in whom atenolol is contraindicated , it should be used in selected patients and hypertensive patients who used atenolol should be followed up continuously for detection of any signs or symptoms that suggesting early or future development of cardiovascular disease.

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