

POTENTIATION OF THE HYPOTENSIVE EFFECT OF CAPTOPRIL BY THE H₂ BLOCKER CIMETIDINE IN THE NORMOTENSIVE ANAESTHETIZED RATS

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ABSTRACT

The effects of captopril (1 mg/kg), cimetidine (25 mg/kg), and their combination on the arterial blood pressure, heart rate, ECG and the calculated double product of anaesthetized normotensive rats were investigated. Results showed that captopril alone but not cimetidine significantly reduced the arterial blood pressure of rats. This effect lasted for 150 min. of administration. Captopril, cimetidine or their combination did not change the heart rate of rats. Administration of captopril in cimetidine-pretreated rats significantly reduced the arterial blood pressure and the calculated double product. Both the intensity and duration of the reduction in blood pressure were significantly greater than that induced by captopril alone, since the duration of this effect was extended for more than 180 min. after administration. This effect had two peaks, the first one came after 30 min. and the second one after 150 min. and the values of these reductions were 24% and 37%, respectively. Conclusively, cimetidine potentiates the hypotensive effect of captopril in anaesthetized rats. The mechanism of this positive interaction may be in part due to that cimetidine may increase the plasma levels of captopril through reduction of its rate of metabolism. This effect may result from the capability of cimetidine to inhibit cytochrome P450 enzymes which may be involved in type I biotransformation of captopril and consequently reduces its rate of degradation.

INTRODUCTION

Almost ever since drugs have been administered to human, there has been an appreciation of the role of metabolism in

influencing the pharmacological effects of these agents. These interactions can be classified into those affecting pharmacokinetics of drug and those affecting its pharmacodynamics⁽¹⁾. Among the pharmacokinetic interactions, is the modification of hepatic metabolism that appears to constitute a major source of drug interactions⁽²⁾. Cimetidine is one of the most widely prescribed drugs and is an effective agent for the treatment of peptic ulcer disease. It has been shown to inhibit hepatic metabolism of a number of drugs in human and there is a great deal of concern about untoward cimetidine-induced pharmacological interactions^(3,4).

It was reported that cimetidine potentiates the hypoprothrombinemic effect of warfarin when given concurrently^(5,6). Subsequent investigations showed reduction in the clearance of theophylline, diazepam, chlordiazepoxide and quinidine when cimetidine was given in combination⁽⁷⁻⁹⁾. Cytochrome P450 is a subfamily of hemoproteins present in the living organisms and concentrated in the liver of human and higher mammals. This group of enzymes play a major role in the metabolism of the endogenous compounds and detoxification of xenobiotic molecules including drugs and environmental pollutants⁽¹⁰⁾. Stimulation or inhibition of cytochrome P450 by certain agents should modify the metabolism of any other drugs and eventually gives rise to drug interaction of clinical significance⁽¹⁾. Cimetidine, the H₂ blocker, was reported to inhibit a large number of liver microsomal enzymes involved in drugs metabolism^(3,4), and have a wide range of affinities for various human liver cytochrome P450⁽¹¹⁾. The interaction of imidazol moiety of cimetidine with the haem moiety of cytochrome P450 is postulated to be responsible for the inhibitory effect of cimetidine for this group of enzymes and consequently on drug metabolism in both human and animals⁽¹²⁾.

Aim of the present study is to assess the possible effects of subacute treatment with cimetidine on the pharmacodynamics of the angiotensin - converting enzyme inhibitor, captopril. Blood pressure, heart rate, ECG parameters and the calculated double

product (rate pressure product) were determined in a trial to investigate the possibility of interactions between the two drugs.

Material and Methods

Adult male Albino rats of local source were used in the present study. Rats were left for access food and water Ad libitum. Animals were divided into four groups (each of 6-8 animals) and were treated with drugs according to the following experimental protocol.

Group I:

Animals of this group were treated with cimetidine (SK&F England) intraperitoneally in a dose of 25 mg/kg for 7 days, and were used to determine the effect of subacute treatment with cimetidine on the cardiovascular system.

Group II:

Animals received captopril (Squibb, Egypt) intraperitoneally, in a dose of 1 mg/kg and were used to study the effect of a single dose treatment of captopril on cardiovascular parameters.

Group III:

Animals of this group were pretreated with cimetidine for 7 days and then received captopril in a single dose and was used to study the effect of combination therapy on the cardiovascular system.

Group VI:

Received solvent and was used as a control.

Determination of the Arterial Blood Pressure:

Arterial blood pressure of rats was determined according to the method of Burden et al(1979)⁽¹³⁾. Rats were anaesthetized using urethane (BDH, England) in a dose of 1.3 g/kg, (this dose was reduced to 1 g/kg in cimetidine pretreated animals). A polyethylene cannulae (PE-50) filled with heparinized glucose (20,000 IU/L of 5% glucose solution) was inserted into the well dissected carotid artery, and the other end of the cannula was connected to blood pressure transducer PT-400.

Determination of the Heart Rate:

The heart rate of rats was determined from the ECG tracing which was recorded using bipolar Lead II cable of ECG. Both the blood pressure transducer and the ECG cables were connected to the Oscillograph (MD-4c-Bioscience Washington) through FC-137 and 123 couplers respectively.

Calculations and Statistical analysis:

Mean arterial blood pressure was calculated as the sum of the diastolic blood pressure and one third of the pulse pressure. The double product (rate pressure product), a parameter that may reflect the oxygen consumption or demand of the myocardium, was calculated by the product of systolic pressure and heart rate⁽¹⁴⁾. The amplitude (mm) and duration (msec) of wave, T wave and QRS complex as well as the duration of PR-and QT-intervals (msec) were calculated.

For all tests, differences were considered to be statistically significant at P value less than 0.05. The findings will be presented as mean value \pm SEM or in some cases as percentage of the initial value. The test of significance was carried out using Student "t" test.

RESULTS

1- Effect on the arterial blood pressure:

Fig(1) showed that captopril in a dose of 1 mg/kg significantly reduced the arterial blood pressure after 15 min of administration. The peak of this reduction was reached after 60 min. recording 15% of the initial value and lasted for 150 min after administration. Cimetidine alone did not change the blood pressure of rats all over the time of the experiment (180 min). Administration of captopril to 7 days-cimetidine - pretreated rats significantly reduced the arterial blood pressure. This effect started 30 min after administration and remained significantly different in comparison with the control

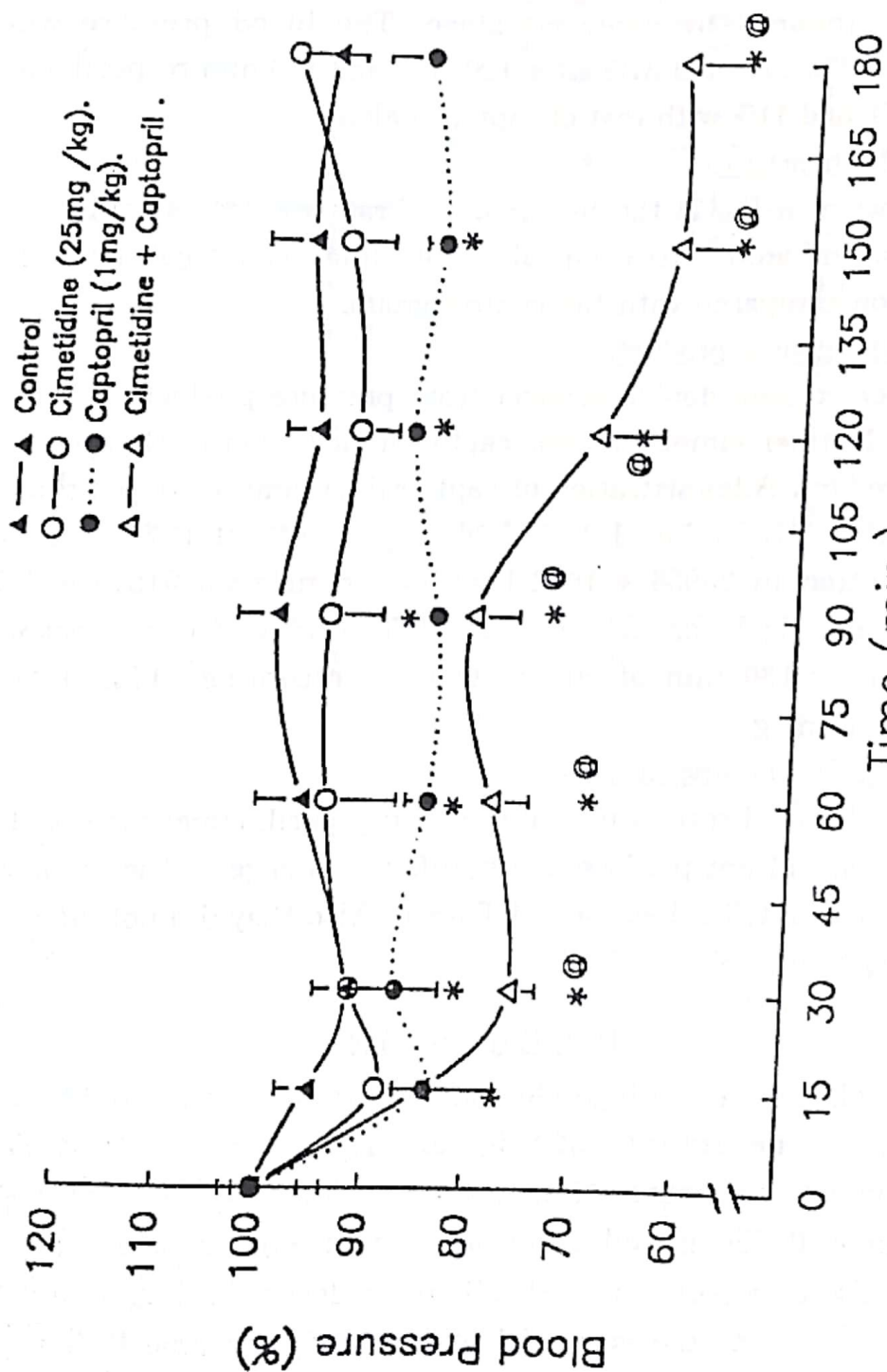


Fig.(1): Effect of cimetidine , captopril and their combination on blood pressure of adult male normotensive rats.

group for more than 180 min. This effect was significantly greater than that produced by captopril alone. The blood pressure was reduced by 30%, 37% and 37% after 120, 150 and 180 min respectively, vs 11%, 14% and 11% with that of captopril alone.

Effect on the heart rate:

As shown in Fig(2) the heart rate of rats was not significantly changed after administration of cimetidine, captopril or their combination compared with the control group.

Effect on the double product:

The calculated double product (rate pressure product) is shown in Fig(3). Neither cimetidine nor captopril significantly changed the double product. Administration of captopril to cimetidine-pretreated rats significantly reduced the double product after 30 min. of administration to 25958 ± 1052 beat/min. mmHg vs. 31875 ± 2679 beat/min. mmHg before administration. The peak of this effect was reached after 180 min of administration recording 21742 ± 2627 beat/min. mmHg.

Effect on ECG parameters:

The obtained results indicated that captopril, cimetidine or their combination did not produce any significant change in the amplitude and duration of QRS, P-wave and T-wave. Also they did not affect the PR-and QT-intervals.

DISCUSSION

The elimination of high clearance drugs may be altered by drugs which alter the activity of microsomal enzyme activities⁽¹⁵⁾. Oxidation reactions are dominant in the metabolism of drugs and cytochrome P 450 mixed function oxidase system was recognized early as the chief contributor⁽¹⁶⁾. Some undesirable drug interactions were attributed to the untoward effects of cytochrome P 450s^(17,18). Stimulation or inhibition of these enzymes can modulate the metabolism and actions of some drugs and other agents⁽¹⁶⁾. Anticonvulsant drugs, (known as enzymes inducers) reduce the bioavailability of lignocaine and paracetamol^(19,20). On the other

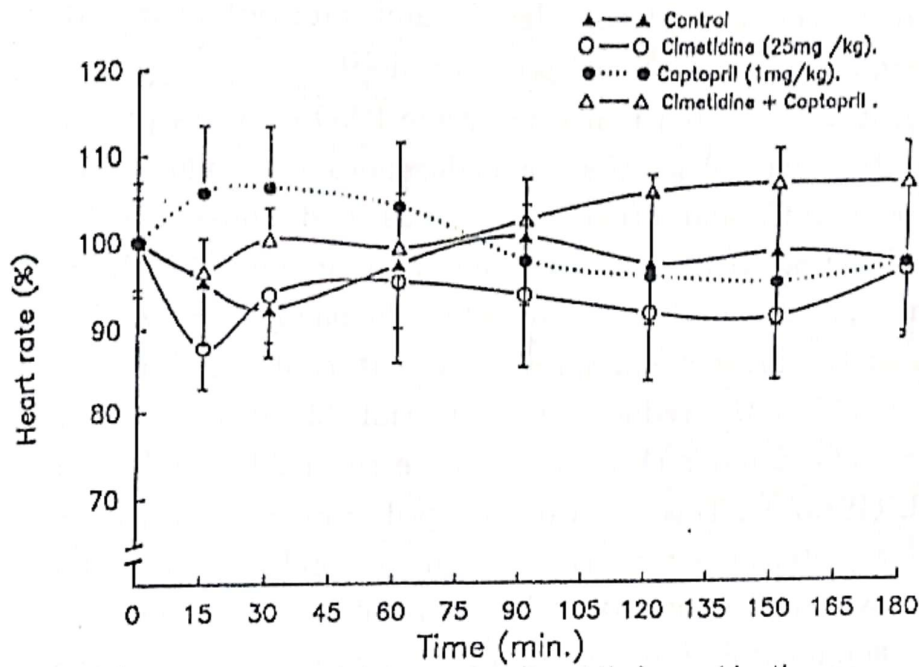


Fig.(2): Effect of cimetidine , captopril and their combination on heart rate of adult male normotensive rats.

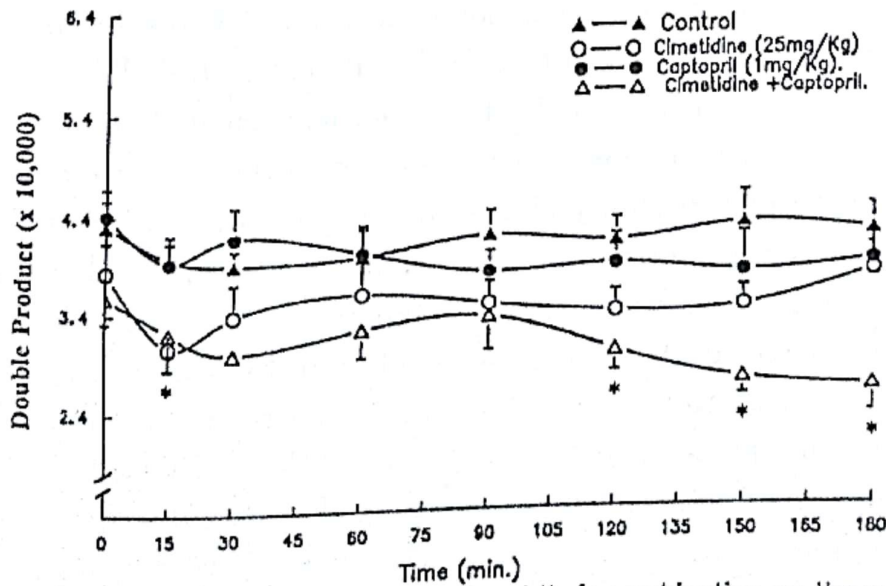


Fig.(3): Effect of cimetidine ,captopril and their combination on the calculated double product of adult male normotensive rats.

hand, inhibition of hepatic microsomal oxidative enzymes by cimetidine increases the plasma levels and bioavailability of theophylline⁽²¹⁾, nifedipine^(22,23) and propranolol⁽²⁴⁾.

Recently, it was reported that cytochrome P450 enzymes play a major role in the metabolism of some endogenous compounds e.g. steroids, prostanoids, and other eicosanoids and consequently, alteration of P450 activities towards some of these substrates have already been implicated in diseases that affect human health⁽²⁵⁾.

Results of the present study revealed that captopril but not cimetidine significantly reduced the arterial blood pressure of normotensive rats. Similar observations were reported by Edwards and Padfield, (1985)⁽²⁶⁾. This effect of captopril is mainly due to the inhibition of angiotensin - converting enzyme⁽²⁷⁾ and in part to the inhibition of sympathetic activities⁽²⁸⁾. Our results also showed that concomitant administration of captopril and cimetidine reduced the arterial blood pressure and double product. Both the intensity and duration of the resultant effects were statistically greater than that induced by captopril alone. This increase in the pharmacodynamic actions of captopril may be partly attributed to the decreased captopril's metabolism and clearance and consequently increased its plasma levels and bioavailability. These findings are in accordance with that reported during concurrent administration of Cimetidine and Nifedipine (21,23), Labetalol⁽¹⁵⁾, Propranolol^(24,29), Chlormethiazol⁽³⁰⁾ and Dilevalol⁽³¹⁾. Those authors found that the increased pharmacodynamic effects of these drugs in the presence of cimetidine may be due to ability of the later for inhibition of liver microsomal oxidative enzymes, cytochrome P450s^(3,4,32,33), resulting in the reduction of the rate of their metabolism, clearance and consequently increasing their plasma level and bioavailability. Captopril was reported to undergo both hepatic and renal clearance through phase I and phase II metabolic pathways^(34,35). Cimetidine, in addition to its inhibitory effect on microsomal oxidative enzyme and phase I metabolism may influence phase II conjugation reactions⁽¹⁵⁾ and reduce liver blood flow⁽²⁹⁾. These effects of

cimetidine may be potentially reduce the rate of captopril metabolism and consequently increase its levels and bioavailability.

Our results showed that captopril alone did not change the double product. These results are not in harmony with that reported by Awan et al 1981⁽³⁶⁾, who found that captopril reduces the double product when given to patients. The discrepancy in the effect obtained by captopril in rats and human beings seems conceivable to be due to species variation. The resulting reduction in the calculated double product induced by the combination of captopril and cimetidine means the reduction in myocardial oxygen demand⁽³⁷⁾. This effect may be due in part to the increased intensity of the reduction of arterial blood pressure in case of cimetidine-pretreated rats compared with the untreated ones.

It was reported that the reduction in the arterial blood pressure leads to the reduction of the effort of the myocardium for the propelling of blood against reduced pressure as well as reduction of the coronary blood flow correlated with a decrease in myocardial oxygen demand. Fortunately, this combination might be beneficial to patients with coronary artery diseases.

From the obtained results it could be concluded that the administration of captopril to cimetidine pretreated rats significantly reduced both the arterial blood pressure and oxygen consumption of myocardium. The intensity and duration of the induced reduction was significantly greater than that produced by captopril alone. The mechanism of this potentiation may be due in part to the inhibition of cytochrome P450 mixed function oxidase enzymes induced by cimetidine, and consequently reduction of the rate of captopril metabolism and clearance and increased its plasma levels and bioavailability. The present investigation suggests that, when it is necessary to prescribe captopril for a patient who is already taking cimetidine, it would seem advisable to make daily check of the arterial blood pressure to adopt the captopril's doses and regimen to avoid the possibility of occurrence severe hypotension and other side effects caused by captopril.

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تعضيد تاثير الكابتوبريل الخافض لضغط الدم بواسطة مشبطات مستقبلات الهيسامين-2 السيميتيدين في الجرزان ذات ضغط الدم الطبيعي

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تم في هذا البحث دراسة تأثير حقن الكابتوبريل (1مجم) والسيميتيدين (25مجم) كلا على حده وكذلك مجتمعان معاً على ضغط الدم الوريدي - معدل ضربات القلب - رسام القلب الكهربائي والنتائج المزدوج في الجرزان ذات ضغط الدم الطبيعي.

وقد أثبتت نتائج هذا البحث أن الكابتوبريل ما ليس للسيميتيدين من تأثيراً خافضاً لضغط دم الجرزان وأن كلاهما على حده ليس له تأثيراً على معدل ضربات القلب ورسام القلب الكهربائي. إن اعطاء الكابتوبريل للجرزان المعالجة مسبقاً بالسيميتيدين أدى إلى إنخفاض في ضغط الدم وكذلك النتائج المزدوج - وأن هذا النقصان يختلف اختلافاً معنوياً من تأثير الكابتوبريل على حده في كلا من قوة التأثير وكذلك مدته وأن هذا التأثير له قمتان أتيا بعد 30 و 150 دقيقة من الحقن مسجلتين 24%, 37% نقصاً مقارنة بالجرزان الغير معالجة.

والخلاصة أن السيميتيدين يقوى من تأثيراً الكابتوبريل الخافض لضغط الدم في الجرزان وأن ميكانيكية هذا التأثير ربما ترجع إلى أن السيميتيدين يزيد من تركيز الكابتوبريل في الدم نظراً لقدرة على تثبيط معدل هدمه بأنزيم السيوكروم ب 450.