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MODULATION OF THE HAEMODYNAMIC AND ELECTROCARDIOGRAPHIC EFFECTS OF NIFEDIPINE BY A CYTOCHROME P-450 ENZYME INHIBITOR

Hassan M. El-Fayoumi, Mohamed N. Zakaria and Salah A. Ghareib

Department of Pharmacology, Faculty of Pharmacy, Zagazig University, Egypt.

ABSTRACT

The effects of a single dose of nifedipine (5 mg/Kg, I.P.) alone, Cimetidine (25 mg/Kg, I.P. for 7 days) alone or their combination on the arterial blood presure, heart rate, the calculated double product, and electrocardiogram (ECG) in anaesthetized normotensive rats have been studied.

Results of the present investigation showed that nifedipine, cimetidine or their combination didn't affect the heart rate. The administration of nifedipine alone produced a significant reduction in arterial blood pressure after 15 min. This effect lasted for 90 min after administration (recording 30% of the initial value). On the other hand, the administration of nifedipine to rats pretreated with cimetidine produced more significant and prolonged reduction in arterial blood pressure, this effect remained to the end of experiment (180 min.). moreover, nifedipine alone produced significant prolongation of PR-and QT intervals. While nifedipine administartion to the rats pretreated with cimetidine produced a significant and continuous prolongation of the PR-interval as well as QT interval and also produced an increase in T-wave amplitude and duration. Cimetidine did not alter any of ECG parameters.

The results of the present study showed that cimetidine potentiates the action of nifedipine on blood pressure and support and extend the previous reports in several models that, cimetidine increases the plasma concentration and consequently the bioavailability of nifedipine due to its characteristic ability to inhibit the liver microsomal enzyme cytochrome P-450.

INTRODUCTION

Nifedipine is a prototype of the dihydropyridine calcium channel blockers. Usually, only the parent compound is active and most of the metabolic steps involve reactions catalyzed by cytochrome P-450 enzymes. Cytochrome P-450 enzymes have been shown to catalyze pyridine formation [1-3].

The highest concentration of cytochrome P-450 in mammals is found in the liver[4], many extrahepatic tissues such as kidney, lung and nasal mucosa also contain significant levels of cytochrome P-450[5].

Nifedipine, being a drug with a high hepatic extraction ratio, has a low oral bioavailability. Consequently, concomitantly administered drugs such as cimetidine, which may potentially inhibit the metabolism of nifedipine may be expected to produce an increase in availability of this agent due to inhibition of the enzymes responsible for the first pass metabolic loss[6].

It is well established that cimetidine inhibits liver enzymes involved in drug metabolism[7-11]. This may sometimes be clinically important, for example plasma theophylline levels have been reported to be increased up to the toxic range when cimetidine is taken concurrently. On these premises, it is of interest to determine whether, on the basis of treatment, there is any modulation in the effect of nifedipine by using a particular H_2-receptor antagonist when prescribed concurrently. Blood pressure, heart rate, ECG parameters and the rate pressure product were measured to give an insight about the haemodynamic effects of nifedipine.

MATERIAL AND METHODS

Adult Wistar rats of either sex, taken from local source and weighing between 300 and 350 g, were used in the present study. Animals had free access to tap water and fed with bread and milk ad libitum. Animals were classified into 4 groups (each of 6-8 rats) according to the drugs received as the following experimental protocol:-

Group I:

In this group, animals were treated with cimetidine 25 mg/kg (I.P) for 7 days to study the effect of cimetidine on the cardiovascular system.

Group II:

Animals were received nifedipine 5 mg/kg (I.P) and used to study the effect of a single dose of nifedipine on the cardiovascular system.

Group III:

Animals of this group were pretreated with cimetidine 25 mg/kg (I.P) for 7 days and then received nifedipine 5 mg/kg in a single dose and were used to study the effect of concurrent administration of these drugs on the cardiovascular system.

Group IV:

In this group, animals were received solvent and used as a control group.

Chemicals:

Chemicals were obtained from the following sources: nifedipine, EPICO, Egypt; cimetidine, SK & F, Egypt, urethane BDH and polyethylene glycol, El-Naser, Egypt and other chemicals of analytical grade E. Merk.

Nifedipine and cimetidine solubility:

Nifedipine as well as cimetidine are water insoluble and were freshly dissolved before injection in polyethylene glycol in all experiments, the final concentration of polyethlene glycol is 0.5% (vol/vol).

Measurements of arterial blood pressure:

Arterial blood pressure was measured according to the method described by Burdine et al.[12], where rats were anaesthetized using urethane (1.3 g/kg), and the dose was reduced in cimetidine pretreated rats to 1 g/kg. A polyethylene cannula (PE-50) full of heparinized glucose (20,000 IU/L in 5% glucose solution) was inserted into the dissected carotid artery, and the other end of the cannula was connected to a blood pressure

transducer PT-400 which connected to the Oscillograph (MD-4C-Bioscience Washington) through FC-137 coupler.

Determination of the heart rate:

Electrocardiogram (ECG) was recorded using bipolar lead II cable and the heart rate was determined from the ECG tracing. The ECG cable was connected to the Oscillograph through 123 coupler.

Calculations and statistical evaluation of the data:

Results were expressed as mean ± SEM or as a percentge of the initial value in some cases. Student's - "t" test for paired or unpaired data was used for statistical evaluation of the data.

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

RESULTS

(1) Effect of cimetidine (25 mg/kg), nifedipine (5 mg/kg) and their combination on the arterial blood pressure:

As shown in Fig. (1), cimetidine in a dose of 25 mg/kg for 7 days did not alter the blood pressure of the rats all over the time of experiments (0-180 min). The same Fig. shows also that, the administration of nifedipine in a single dose of 5 mg/kg significantly reduced the arterial blood pressure after 15 min of administration recording 13% of the initial value. The peak was reached after 60 min recording to 30% of the initial

value and lasted for 90 min after administration. Administration of nifedipine to rats pretreated with cimetidine for 7 days significantly reduced the arterial blood pressure. This effect started after 15 min of administration and remained significantly different compared with the control group and lasted for 180 min (the experimental time). The duration of the hypotensive effects of nifedipine in cimetidine pretreated rats was, longer than that of nifedipine alone.

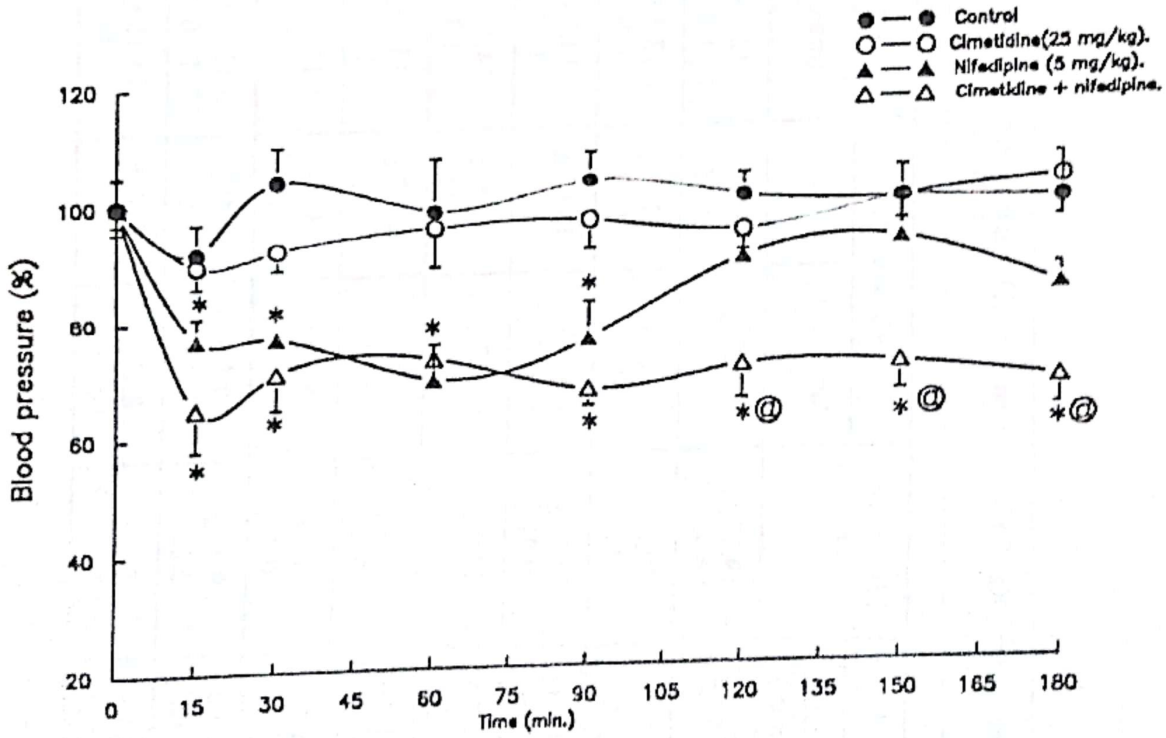

Fig.(1): Effect of cimetidine, nifedipine and their combination on blood pressure of adult male normotensive rats .

* Significantly different from control values at p<0.05

@ Significantly different from nifedipine treated group at p<.05.

Table (1): Effect of cimetidine (25mg/Kg for 7 days) on the ECG parameters of adult male normotensive rats

Time interval	P-wave		PR-interval (msec)	QRS- complex		ST-Segment (msec)	T-wave		QT- interval (APD) (msec)
	Amplitude (mm)	duration (msec)		Amplitude (mm)	duration (msec)		Amplitude (mm	duration (msec)	
0	1.41± 0.20	21.7± 1.66	19.17±. 0.84	7.67± 0.42	16.67± 1.05	12.5± 1.7	4.5± 0.42	36.6± 3.33	78.3± 3.06
15	1.5± 0.31	21.70± 1.66	20.0± 0.0	7.83± 0.60	17.5± 1.11	13.3± 1.66	4.5± 0.49	38.3± 4.01	76.7± 2.1
30	1.5± 0.25	21.70± 1.66	19.17± 0.81	8.0± 0.57	16.67± 1.05	13.3± 1.66	4.5± 0.49	38.3± 4.01	76.7± 4.21
60	1.41± 0.23	21.7± 1.66	20.0± 0.0	7.67± 0.55	17.5± 1.11	14.16± 2.0	4.16± 0.60	36.6± 2.11	76.7± 4.21
90	1.41± 0.03	21.7± 1.66	20.0± 0.0	8.0± 0.61	16.67± 1.05	13.3± 1.66	4.3± 0.61	38.3± 3.06	80.0± 4.45
120	1.33± 0.16	21.7± 1.66	20.0± 0.0	8.0± 0.72	15.8± 0.83	12.5± 1.1	4.0± 0.57	35.0± 2.23	76.7± 4.21
150	1.33± 0.24	21.7± 1.66	19.17± 0.81	7.8± 0.60	16.67± 1.05	13.3± 1.66	3.83± 0.7	35.0± 2.23	71.7± 3.07
180	1.33± 0.24	18.3± 1.05	18.3± 1.05	8.17± 0.73	16.67± 1.05	14.16± 2.0	3.67± 0.55	35.0± 2.23	73.3± 5.55

Table (2): Effect of nifedipine (5mg/Kg) on the ECG parameters of adult male normotensive rats

Time interval	P- wave		PR-interval. (msec)	QRS- complex		ST-Segment (msec)	T-wave		QT- interval (APD) (msec)
	Amplitude (mm)	duration (msec)		Amplitude (mm)	duration (msec)		Amplitude (mm)	duration (msec)	
0	1.00± 0.12	23.3± 2.1	16.67±. 2.10	11.4± 1.45	20.0± 0.0	10.8± 0.83	5.4± 0.37	51.6± 4.77	85.0± 3.41
15	1.08± 0.08	21.6± 1.66	23.3± 2.10*	9.7± 1.23	18.3± 1.66	10.0± 0.0	5.6± 0.42	53.3± 43.21	95.0± 4.27
30	0.91± 0.08	25.0± 2.23	21.6± 01.66	11.3± 1.23	20.0± 0.0	11.6± 1.66	5.3± 0.71	53.3± 3.33	93.3± 3.33
60	0.91± 0.153	25.0± 3.44	28.3± 3.06*	10.5± 1.09	20.0± 0.0	13.3± 2.1	6.1± 0.73	53.3± 4.21	96.6± 4.94
90	1.08± 0.20	25.0± 2.23	25.0± 2.23*	10.7± 1.35	20.0± 0.0	15.0± 3.41	7.2± 0.86	53.3± 2.10	95.0± 2.23*
120	0.90± 0.09	24.0± 2.23	22.0± 1.82	9.7± 0.78	18.0± 1.82	12.0± 1.82	6.8± 1.00	52.0± 1.82	96.0± 3.65
150	0.80± 0.11	22.0± 1.82	24.0± 2.23*	10.8 0.98	22.0± 1.82	14.0± 2.23	6.4± 1.31	50.0± 2.88	90.0± 2.88
180	0.87± 0.10	22.5± 2.04	27.5± 2.04*	10.0± 1.11	17.5± 2.5	12.5± 2.04	5.5± 0.23	50.0± 3.33	95.0± 5.26

* Significant at $P < 0.05$.

Table (3): Effect of nifedipine (5mg/Kg) in combination with cimetidine (25mg/Kg for 7 days) on the ECG parameters of adult male normotensive rats

Time interval	P- wave		PR-interval (msec)	QRS- complex		ST-Segment (msec)	T-wave		QT- interval (APD) (msec)
	Amplitude (mm)	duration (msec)		Amplitude (mm)	duration (msec)		Amplitude (mm)	duration (msec)	
0	0.708± 0.135	23.3± 2.11	15.83±. 2.00	12.08± 1.54	17.5± 1.71	10.0± 0.0	3.08± 0.27	36.67± 2.11	76.7± 3.33
15	0.625± 0.125	20.0± 0.0	20.0± 0.0	11.8± 1.57	18.3± 1.66	10.8± 0.83	1.75± 0.335*	36.67± 3.33	80.0± 4.47
30	0.625± 0.125	22.0± 1.82	22.0± 1.825	12.5± 1.282	19.1± 0.83	10.0± 0.0	2.0± 0.339*	38.3± 1.66	78.3± 4.77
60	0.792± 0.261	21.67± 1.665	26.67± 2.10*	12.0± 1.13	20.0± 0.0	13.3± 2.1	3.17± 0.46	41.67± 3.07	90.0± 2.58*
90	0.500± 0.112	27.5± 3.90	26.67± 2.10*	11.9± 1.55	20.0± 0.0	11.7± 1.67	2.91± 0.62	43.3± 3.33	86.6± 2.1*
120	0.625± 0.102	25.0± 2.233	30.0± 3.33*	10.5± 1.84	20.0± 0.0	15.0± 2.35	3.25± 0.51	47.5± 2.03*	87.5± 3.87
150	0.875± 0.256	20.0± 0.0	25.0± 3.41*	11.25± 1.68	20.0± 0.0	11.7± 1.67	2.67± 0.49	45.0± 2.23*	93.3± 4.94*
180	0.916± 0.345	26.67± 2.11	28.3± 3.07*	11.3± 1.57	20.0± 0.0	11.7± 1.67	2.33± 0.35	45.0± 2.23*	90.0± 3.63*

* Significant at $P < 0.05$

2- Effect of cimetidine, nifedipine and their combination on the heart rate:

Fig. (2) shows that, the administration of cimetidine (for 7 days) alone, nifedipine alone, or administration of nifedipine to rats pretreated with cimetidine, did not significantly change the heart rate of rats compared with the control group.

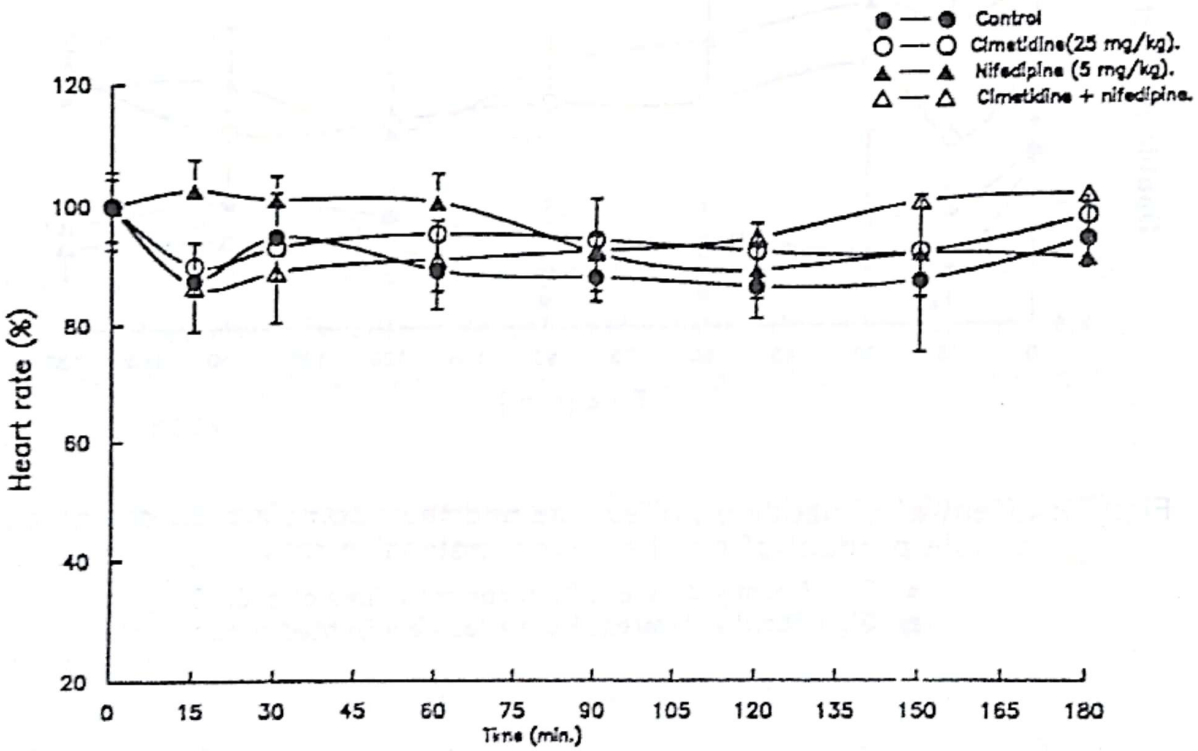

Fig.(2): Effect of cimetidine, nifedipine and their combination on heart rate of adult male normotensive rats .

3- Effect of cimetidine, nifedipine and their combination on the double product:

As presented in Fig. (3), neither cimetidine nor nifedipine has produced significant change in the double product. Administration of nifedipine in cimetidine pretraeted rats significantly reduced the double product. This effect lasted for 90 minutes.

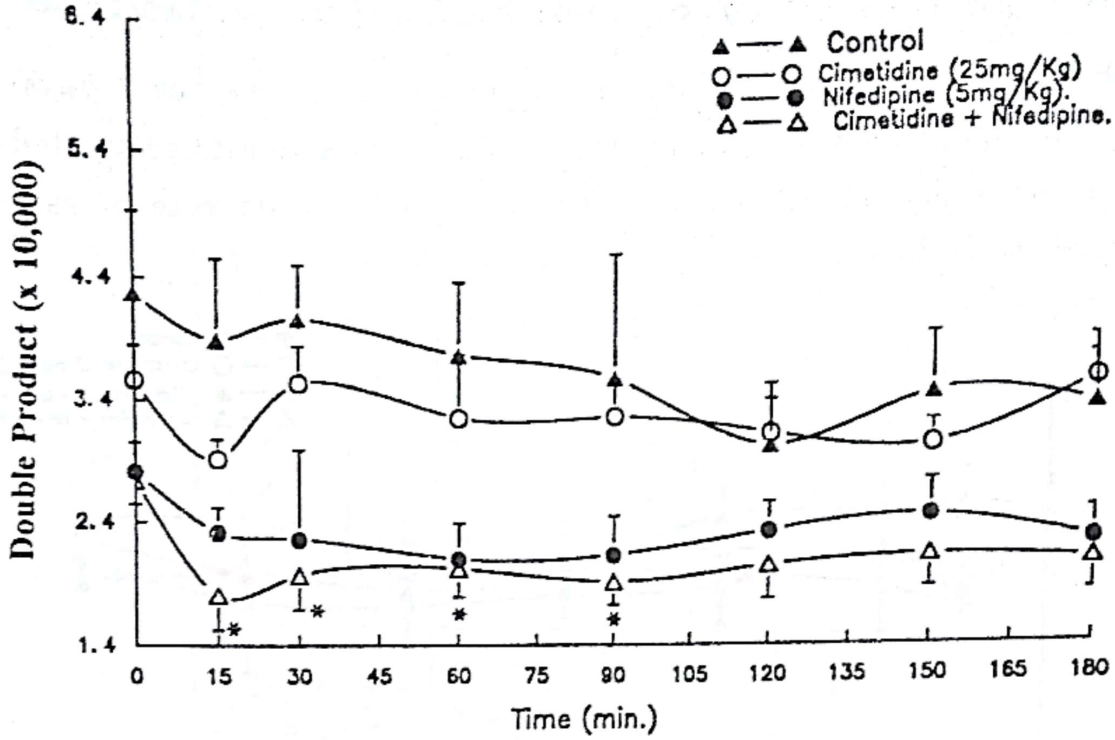

Fig.(3): Effect of cimetidine , nifedipine and their combination on the calculated double product of adult male normotensive rats.

* Significantly different from control values at p<0.05
@ Significantly different from nifedipine treated group at p<.05

4- Effect of cimetidine, nifedipine and their combination on the electrocardiographic parameters:

As shown in Table (1), the administration of cimetidine alone for seven days had no significant efect on the P-wave, PR-interval, QRS complex, ST segment, T-wave (duration & amplitude) and QT interval.

Table (2) shows that nifedipine when administered alone produced a significant prolongation of the PR-interval after 15,60,90,150-180 min of administration. Also significant increase in QT interval (the action potential duration) was produced after 90 min. of administration.

The administration of nifedipine to rats pretreated with cimetidine for seven days, induced a significant and continuous (monophasic) prolongation of the PR-interval as well as QT-interval after 60,90,120,150 and 180 min of administration.

Nifedipine administration in rats pretreated with cimetidine also produced an increase in T-wave amplitude and duration (15 & 30 min. and 120-180 min.), respectively (Table 3).

DISCUSSION

Cimetidine inhibit s hepatic microsomal oxidative drug metabolism. Previous reports suggest that clearance of several oxidatively metabolized drugs in humans including antipyrine, diazepam, chlordiazepoxide, warfarin, theophylline and caffeine is impaired during cimetidine treatment[13-16].

In this situation, it has been reported that nifedipine oxidation can be inhibited by cimetidine in vivo[17], and cytochrome P-450 III A4 appears to be one of the cytochrome enzyme most sensitive to this compound.

Results of the present study showed that the administration of nifedipine in a single dose produced reduction in the arterial blood pressure. This result is in agreement with that of Opie and White[18], and this effect may be due to the vasodilator effect of nifedipine which acts as a calcium channel blocking agent. The results of the present study also reveals that the administration of nifedipine to rats pretreated with cimetidine induces a significant reduction in the arterial blood pressure. The duration of this reduction was greater than that of nifedipine alone. This result is in agreement with that of Kirch et al.[19] who suggested that nifedipine level is considerably increased in the presence of cimetidine and that this causes a pharmacodynamic effect in hypetensive patients,

the combination produces a significantly greater reduction in blood pressure than nifedipine alone.

On the other hard, it was reported that there was no potentiation of the action of nifedipine when concomitantly administered with cimetidine and the marked increase in circulating plasma nifedipine concentration during cimetidine administration can not be translated into a statistically significant potentiation of pharmacological activity [6]. Moreover, Smith et al.[20] suggested also that cimetidine produces a significant increase in the area under the curve (AUC) of both single and steady state dosing of nifedipine. Peak nifedipine levels were significantly increased only in the chronic dose study compared to placebo.

In the present study, cimetidine had no significant effect on any of the electrocardiographic parameters but potentiated the effects of nifedipine on the ECG.

The administration of nifedipine alone has significantly prolonged the PR-interval, a typical character of calcium channel blockers as calcium plays the major role in the cardiac action potential in the sinoatrial and atrioventricular nodes. This effect which reflects delayed condition through the AV node was biphasic. The prolongation of the PR-interval was continuous (monophasic) when nifedipine was given to rats pretreated with cimetidine for seven days. Pretreatment with cimetidine has prolonged the duration of the increase in QT interval (the action potential duration) produced by nifedipine alone after 90 minutes reflecting that the increase in intensity and duration of the action of nifedipine might be due to increased plasma level of nifedipine.

On the other hand, nifedipine when given to rats pretreated with cimetidine has prolonged the duration of the T-wave indicating reduced efflux of potassium through phase 3 of repolarization. This effect which appeared 2 hours after nifedipine administration and lasted to the end of

the experiment and has not been produced by administration of nifedipine alone, suggests a higher plasma levels of nifedipine in presence of cimetidine treatment. This higher plasma concentration of nifedipine may exert a blocking activity to potassium channels leading to prolonged duration of T-wave (efflux of K^+ during phase 3 of repolarization) and consequently prolonged QT-interval (action potential duration). Since cimetidine is known as an agent that inhibits the liver microsomal oxidative enzyme, cytochrome P-450[21-23] it can be suggested that, the increase in pharmacodynamic effects of nifedipine in the presence of cimetidine may be due to the ability of cimetidine to inhibit this enzyme.

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تعديل تأثيرات النيفيدبين الدموديحركية وعلى رسم القلب الكهربائى بواسطة مثبط لأنزيم السيتوكروم ب ٤٥٠

حسن محمود محمد الفيومى - محمد نجيب محمد زكريا

وصلاح عبد المنعم غريب

قسم الفارماكولوجى - كلية الصيدلة - جامعة الزقازيق

فى هذا البحث تم دراسة تأثيرات النفيدبين (٥ مجم/كجم) منفرداً ، السيميتيدين (٢٥ مجم/كجم لمدة ٧ آيام) منفرداً أو كليهما معا على ضغط الدم الشريانى ومعدل ضربات القلب والناتج الثنائى المعين ورسم القلب الكهربائى فى الجرذان المخدرة ذات ضغط الدم الطبيعى.

بينت نتائج هذا البحث أن أى من النفيدبين والسيميتيدين منفردين أو كليهما معا لم يؤثر على معدل ضربات القلب . أدى إعطاء النيفيدبين منفرداً إلى انخفاض ملوحظ فى ضغط الدم الشريانى بعد ١٥ دقيقة بينما أدى أعطاء النيفيدبين إلى جرذان سبق اعطائهم السيميتيدين إلى انخفاض أقوى وأطول فى المدة فى ضغط الدم الشريانى وقد استمر هذا التأثير حتى نهاية التجربة (١٨٠ دقيقة) . بالإضافة إلى هذا فقد أحدث النيفيدبين زيادة فى فترتى الإ PR و QT. بينما أدى اعطاء النيفيدبين إلى جرذان سق علاجها بالسيميتدين إلى زيادة ملحوظة ومستمرة فى فترتى الـ PR والـ QT وأيضاً أحدث زيادة فى ارتفاع وطول مدة حدوث موجة الـ T . لم يغير السيميتدين فى أى من مكونات رسم القلب الكهربائى .

تبين نتائج هذه الدراسة أن عقار السيميتيدين يعضد من تأثير عقار النيفيدبين كما تؤكد وتكمل الدراسات السابقة المختلفة التى تبين أن السيميتيدين يزيد من تركيز النيفيدين فى البلازما وبالتالى يزيد من أتاحته الحيوية نتيجة مقدرته المميزة على تثبيط أنزيم الكبد الكروموسومى السيتوكروم ب ٤٥٠ .