A randomized comparative trial of first-dose response to Angiotensin-Converting Enzyme Perindopril and Captopril in Indonesian heart failure patients

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Abstrak

Beberapa penelitian besar dengan kontrol plasebo telah menunjukkan bahwa obat-obat penghambat enzim pengubah angiotensin (ACE inhibitors) secara bermakna mengurangi mortalitas dan morbiditas semua kelas fungsional gagal jantung kongestif, namun hanya sebagian kecil pasien yang mendapat pengobatan penghambat ACE tersebut. Salah satu kendala adalah terjadinya hipotensi dosis awal pada beberapa pasien. Suatu penelitian acak, tersamar-ganda, terapi dosis tunggal, dengan kelompok paralel dilakukan dengan tujuan membandingkan respons dosis awal terhadap penghambat ACE captopril dan perindopril dosis rendah pada pasien gagal jantung kronik yang stabil. Tujuh puluh pasien (New York Heart Association class I-IV) dimasukkan kedalam penelitian. Tekanan darah diukur setiap 15 menit 2 jam sebelum pemberian obat. Hasil rata-rata tersebut diambil sebagai tekanan darah dasar. Pasien diacak untuk menerima dosis tunggal perindopril 2 mg atau captopril 6,25 mg. Setelah obat diminum, tekanan darah dimonitor setiap 15 menit selama 2 jam, setiap 30 menit selama 5 jam, selanjutnya setiap jam untuk 2 jam kemudian. Penurunan maksimum tekanan arteri rata-rata adalah 0,85 mmHg untuk perindopril dan 4,60 mmHg untuk captopril. Penurunan maksimum sistolik 3,31 mmHg untuk perindopril dan 6,76 mmHg untuk captopril sedang penurunan maksimum diastolik 1.08 mmHg untuk perindopril dan 2.63 mmHg untuk captopril. Efek hipotensif captopril dimulai segera setelah pemberian obat dan mencapai maksimum setelah 1 sampai 2 jam sedang perindopril memperlihatkan sedikit penurunan sistolik setelah 1 jam dan sedikit penurunan diastolik setelah 4 jam. Dibanding captopril, perindopril memperlihatkan kecenderungan minimal untuk menyebabkan hipotensi dosis awal pada pasien gagal jantung. ***(Med J Indones 2002; 11: 19-23)***

Abstract

Several large placebo-controlled trials have confirmed that angiotensin converting enzyme (ACE) inhibitors significantly reduce mortality and morbidity in all functional grades of congestive heart failure (CHF), nevertheless only a proportion of patients who may benefit from treatment are prescribed an ACE inhibitor. One of the perceived difficulties is the occurrence of first-dose hypotension in susceptible patients. A double-blind, randomised, single-dose therapy, parallel-group study was conducted with the aim to compare the first-dose responses to low dose ACE inhibitors captopril and perindopril in patients with stable chronic heart failure. Seventy patients (New York Heart Association class I-IV) were included. Blood pressure was recorded every 15 minutes 2 hours before starting treatment. The mean of these readings was taken as the baseline blood pressure. Patients were randomised to receive a single-dose of captopril 6.25 mg or perindopril 2 mg. After taking the drug, blood pressure was monitored every 15 minutes for 2 hours, every 30 minutes during 5 hours then hourly after 2 hours. The maximum mean arterial pressure fall from baseline of perindopril was 0.85 mmHg compared to captopril 4.60 mmHg. The maximum mean systolic fall from baseline of perindopril was 3.31 mmHg compared to captopril 6.76 mmHg while the maximum mean diastolic fall from baseline of perindopril was 1.08 mmHg compared to captopril 2.63 mmHg. The hypotensive effect of the captopril group started soon after dosing and reached its maximum after 1 to 2 hours while perindopril showed slight reduction of systolic after 1 hour and slight reduction of diastolic after 4 hours. Compared to captopril, perindopril seemed to be less likely to cause first-dose hypotension in patients with heart failure. ***(Med J Indones 2002; 11: 19-23)***

Keywords*: first dose hypotension, perindopril, captopril, chronic heart failure*

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ACE inhibitors was first discovered to treat hypertension. Through the inhibition of Angiotensin Converting Enzyme the formation of Angiotensin II from Angiotensin I is inhibited. Then it is shown that ACE is not only found in the blood circulation, but also in the tissues, including the myocardium. Relating to that, many studies have been conducted with ACE inhibitors which showed that it can prevent the remodelling of myocardium.

Currently ACE inhibitor is the drug-of-choice for heart failure. Several large placebo-controlled trials for more than 10 years have confirmed that ACE inhibitors significantly reduce mortality and morbidity in all functional grades of congestive heart failure, as it also reduce mortality following acute myocardial infarction. Nevertheless, only a proportion of patients who may benefit from treatment are prescribed ACE inhibitor. Two USA studies showed only 30-40% heart failure patients were given ACE inhibitor. One of the perceived difficulties of introducing ACE inhibitors in clinical practice is the incidence of first-dose hypotension in susceptible patients. Heart failure patients often present low blood pressure, thus if given first dose ACE inhibitor, may reduce blood pressure which will then decrease tissue perfusion. Several clinical trials have reported 2-33% incidents of symptomatic first-dose hypertension which depend upon the dosage. Several risk factors are hyponatremia, hypovolemia caused by diuretics, low systolic blood pressure (<100 mmHg), low renin level or high aldosteron level and renal insufficiency. Risk factors also could be determined upon the dosage, different ACE inhibitors, duration of action and the severity of heart failure. Based on that, this is study was conducted with the asumption that not all ACE inhibitors cause first-dose hypotension. The aim was to compare the first-dose responses to low dose ACE inhibitors captopril and perindopril in patients with stable chronic heart failure.

METHOD

The study was a comparative, double-blind, randomised, single-dose therapy with parallel group. A 5 mmHg difference (SD±12 mmHg) in the drop of mean arterial blood pressure between the perindopril and the capropril group is considered clinically relevant. In order to be able to show such a difference with an α risk of 5% and a reasonable power (β between 75 and 96%), the total number of patients must lie between 160 and 320 patients. However we were only able to recruit seventy chronic heart failure patients who visited the cardiology polyclinics confirmed by clinical history, examination and ECG and has the indication for an ACE inhibitor.

Inclusion criteria

- Heart failure NYHA (New York Heart Association) class I-IV
- Resting heart rate 60-130 beat per minute in supine position
- Diuretics discontinued minimal 24 hours before treatment
- Age >18 years
- Written informed consent given to participate

Exclusion criteria

- Unstable clinical condition
- Systolic blood pressure <100 mmHg
- Unstable angina, Acute myocardial infarction
- Aortic stenosis
- Stroke in the previous 3 months
- Chronic Pulmonary Obstructive Disease
- Known hepatic or renal insufficiency
- Known hypersensitivity to ACE inhibitors
- Administration of any ACE inhibitor prior to inclusion to the study within 5 half-lives of that ACE inhibitor
- Concomitant treatment with any one of the following: monoamine oxidase inhibitors, neuroleptics, lithium, potassium-sparing diuretics, potassium salts
- Pregnant or lactating women or those of child bearing potential without effective contraception (oral contraceptive pill or intra-uterine device)

Study Procedure

Blood pressure was monitored every 15 minutes for 2 hours before treatment. The mean of these readings was taken as the baseline blood pressure. Patients were randomised to receive a single-dose of perindopril 2 mg or captopril 6.25 mg. After taking the drug, blood pressure was monitored every 15 minutes during 2 hours, every 30 minutes for the subsequent 5 hours and then hourly for the last one hour. During this study period, patients remained supine.

First-dose hypotensive response is a considerable fall in blood pressure in response to the first dose of ACE inhibitors in patients with heart failure. This study is design to indicate the difference in the acute response to ACE inhibitors. From a Malaysian experience, the changes were more marked in the captopril group at

1.5 and 2 hours, whereas in the enalapril group it was marked at 4 and 5 hours.

Statistical Analysis

The mean of the first eight readings was taken in order to establish the stabilized baseline value. Baseline blood pressure assessment is very important since all the subsequent values will be compared to that baseline value. That's why it is necessary to assess every 15 minutes for two hours, before drug ingestion (Malaysian experience).(6) The major variables were systolic (SBP) and diastolic blood pressure (DBP). Mean arterial pressure (MAP) was calculated by the standard formula :

$$MAP = DBP + \frac{(SBP - DBP)}{3}$$

Statistical analysis with unpaired t-test was performed to evaluate the first-dose response between perindopril and captopril and to compare the changes of blood pressure over time between the two drugs. All data are presented as mean ± standard deviation.

RESULTS

Patient characteristics

There were seventy patients examined consisted of 48 males and 22 females (68.8 : 31.4%). The randomised group of patients had similar age, bodyweight and severity of heart failure (NYHA class) as seen on Table 1 below.

Table 1. Patient characteristics

Characteristics	Perindopril n=35	Captopril n=35	p value
Sex			1.000
Male	24 (68.6%)	24 (68.6%)	
Female	11 (31.4%)	11 (31.4%)	
Age	59.3 ± 11.9	56.1 ± 14.5	0.325
Body weight	57.6 ± 13.6	60.8 ± 11.7	0.299
Height	159.3 ± 17.7	162.0 ± 7.0	0.305
NYHA Class			0.764
I	1 (2.9%)	2 (5.7%)	
II	18 (51.4%)	19 (54.3%)	
III	6 (17.1%)	5 (14.3%)	
IV	9 (25.7%)	9 (25.7%)	

The mean systolic baseline of perindopril was 126.81 mmHg and captopril 132.7 mmHg. The maximum systolic fall from baseline during the 8 hours of monitoring was 3.71 mmHg for perindopril compared to 7.71 mmHg for captopril (Table 2).

The mean diastolic baseline of perindopril was 80.1 mmHg and captopril 81.2 mmHg. The maximum diastolic fall from baseline during the 8 hours of monitoring was 2.48 mmHg for perindopril compared to 3.18 mmHg for captopril (Table 3).

The mean arterial pressure baseline of perindopril was 95.60 mmHg and captopril 98.1 mmHg. The maximum MAP fall from baseline during the 8 hours of monitoring was 0.85 mmHg for perindopril compared to 4.60 mmHg for captopril (Table 4, Figure 1).

Table 2. Comparison of Systolic Blood Pressure between Perindopril and Captopril

	Perindopril (n=35)	Captopril (n=35)
Time of Observation	Mean Blood Pressure ± SD (mmHg)	Mean Blood Pressure ± SD (mmHg)
Blood pressure (H-2-H0)	126.8	132.7
H0-H2 (every 15 min)		
H0 1	126.3 ± 16.8	129.1 ± 18.0
H0 2	124.6 ± 17.4	130.0 ± 19.3
H0 3	123.9 ± 18.3	126.7 ± 19.4
H0 4	123.1 ± 19.1	125.9 ± 19.3
H1 1	124.0 ± 18.7	126.6 ± 19.8
H1 2	124.9 ± 17.7	126.9 ± 18.3
H1 3	127.3 ± 19.1	125.0 ± 16.0
H1 4	123.4 ± 26.5	125.3 ± 18.9
H2-H7 (every 30 min)		
H2 1	126.0 ± 18.0	128.9 ± 18.9
H2 2	126.3 ± 15.4	127.7 ± 19.8
H3 1	125.4 ± 16.2	128.1 ± 18.7
H3 2	124.3 ± 17.2	128.7 ± 18.9
H4 1	125.6 ± 16.9	127.3 ± 19.4
H4 2	124.9 ± 16.9	128.6 ± 18.8
H5 1	126.3 ± 19.0	130.1 ± 16.7
H5 2	126.0 ± 18.3	131.0 ± 17.5
H6 1	127.0 ± 18.8	131.9 ± 19.1
H6 2	127.0 ± 17.3	129.1 ± 18.9
H7-H8		
H7	128.9 ± 18.2	134.7 ± 21.8
H8	131.4 ± 19.9	135.6 ± 21.7

Table 3. Comparison of Diastolic Blood Pressure between Perindopril and Captopril

Time of Observation	Perindopril (n=35) Mean Blood Pressure ± SD (mmHg)	Captopril (n=35) Mean Blood Pressure ± SD (mmHg)
Blood pressure (H-2-H0)	80.1	81.2
H0-H2 (every 15 min)		
H0 1	80.6 ± 10.6	81.6 ± 14.5
H0 2	80.4 ± 10.6	80.4 ± 14.3
H0 3	80.3 ± 10.4	79.1 ± 14.2
H0 4	78.9 ± 13.0	79.4 ± 13.4
H1 1	77.6 ± 13.6	78.6 ± 13.8
H1 2	79.9 ± 12.6	78.0 ± 12.8
H1 3	80.6 ± 12.6	79.0 ± 12.8
H1 4	81.7 ± 11.0	78.6 ± 13.8
H2-H7 (every 30 min)		
H2 1	79.6 ± 11.5	79.6 ± 13.2
H2 2	79.0 ± 11.7	79.4 ± 13.9
H3 1	79.1 ± 11.2	80.3 ± 14.0
H3 2	78.9 ± 9.9	80.7 ± 15.0
H4 1	78.1 ± 10.4	79.6 ± 14.2
H4 2	79.1 ± 10.1	80.9 ± 16.0
H5 1	77.9 ± 11.6	81.3 ± 14.9
H5 2	78.3 ± 12.9	82.0 ± 15.2
H6 1	79.1 ± 11.5	82.1 ± 17.1
H6 2	80.0 ± 11.1	79.4 ± 16.4
H7-H8		
H7	78.9 ± 11.6	82.1 ± 16.0
H8	82.0 ± 11.3	81.7 ± 15.0

Table 4. Comparison of Mean Arterial Pressure between Perindopril and Captopril

Time of Observation	Perindopril (n=35) Mean Blood Pressure ± SD (mmHg)	Captopril (n=35) Mean Blood Pressure ± SD (mmHg)
Blood pressure (H-2-H0)	95.6	98.1
H0-H2 (every 15 min)		
H0 1	96.7 ± 11.1	96.9 ± 13.9
H0 2	95.9 ± 11.1	96.5 ± 13.6
H0 3	95.7 ± 11.1	93.8 ± 12.8
H0 4	94.4 ± 13.5	94.2 ± 11.9
H1 1	93.8 ± 14.5	94.0 ± 13.1
H1 2	95.6 ± 13.1	93.8 ± 12.4
H1 3	96.7 ± 13.5	93.2 ± 11.2
H1 4	95.8 ± 13.7	93.2 ± 12.9
H2-H7 (every 30 min)		
H2 1	95.9 ± 12.1	95.2 ± 12.4
H2 2	95.2 ± 12.0	95.1 ± 13.8
H3 1	95.1 ± 11.7	95.8 ± 13.3
H3 2	94.4 ± 11.5	95.7 ± 14.8
H4 1	94.5 ± 11.4	94.9 ± 14.3
H4 2	94.6 ± 11.1	96.6 ± 15.2
H5 1	94.3 ± 12.8	96.7 ± 13.7
H5 2	94.3 ± 13.8	98.0 ± 13.4
H6 1	95.1 ± 12.8	98.2 ± 15.6
H6 2	95.8 ± 12.0	95.9 ± 15.6
H7-H8		
H7	95.7 ± 12.5	99.9 ± 15.3
H8	99.0 ± 13.3	100.4 ± 15.0

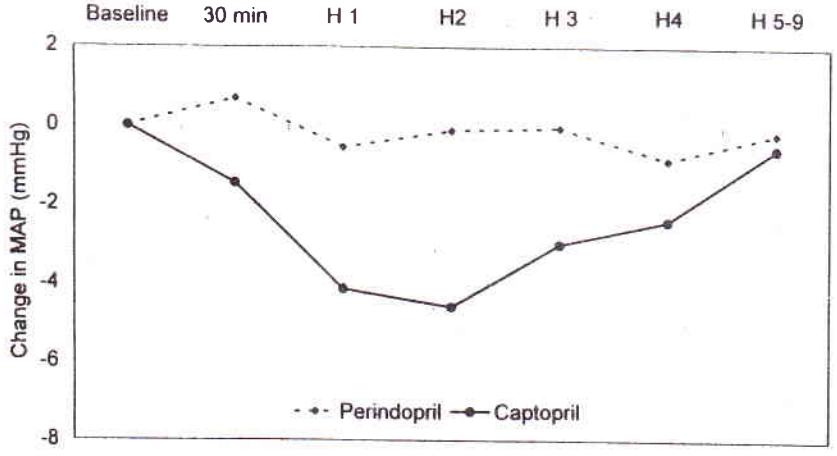

Figure 1. Mean peak blood pressure fall after a single dose in 70 patients with congestive heart failure

DISCUSSION

In this study the standard ACE inhibitor, captopril was compared to the long-acting perindopril, to evaluate the different responses to the early phases of blood pressure reduction. The characteristic baseline data of both groups were comparable.

In the perindopril group, this study showed that the maximum fall in systolic compared to baseline value was at 1 hour (3.31 mmHg) while for captopril was at 2 hours (6.76 mmHg). The maximum fall in diastolic compared to baseline value was at 4 hours for perindopril (1.08 mmHg) and at 2 hours for captopril (2.63 mmHg). The maximum fall in mean arterial pressure from baseline was at 4 hours for perindopril (0.85 mmHg) and 2 hours for captopril (4.60 mmHg). Whereas in the perindopril group the hypotensive effect was not so marked, the slight reduction was seen in systolic at 1 hour and diastolic at 4 hours.[6]

In the study done by Navookarasu, et al in Malaysia comparing the first-dose respone of several ACE inhibitors, it was shown that at 1.5 – 2 hours the reduction in the captopril group was significant, while for perindopril the blood pressure response was almost parallel to the placebo group.[2]

In a study by Lechat who used several ACE inhibitors for chronic heart failure patients, the perindopril group did not show marked hypotensive effect, no patient was withdrawn from treatment due to orthostatic hypotension.

The mechanism of the occurrence of first-dose hypotension in ACE inhibitors is not yet clear. Several hypothesis are (1) reduced venous return caused by indirect inhibition of sympathetic tone which was produced by the lowering level of angiotensin II leading to the reduction in the tone of vein. (2) Bezhold-Jarisch vagal reflex caused the hypotension and bradycardia.

There is also a presumption that the first-dose hypotension occur frequently in patients with renovascular hypertension or to those who is being treated with diuretics. Also in patients with hypovolemia or hyponatremia. Besides that there is also the competitive effect between the drug and its metabolite in the ACE binding site in tissues. Perindopril has a lipophilic effect, thus it shows a significant concentration in tissues and will precede the metabolite perindoprilat, in binding ACE tissues. In heart failure cases, the production of perindoprilat was slowed, leaving perindopril to bind ACE first in tissues.

In this study, the number of patients recruited were not enough to show any significant differences between the two products. So there was only a tendency shown in this study. Perindopril showed a slight reduction in systolic pressure at 1 hour but not as much as captopril. While for diastolic, captopril showed reduction at 2 hours compared to perindopril which occurred at 4 hours. The MAP of perindopril did not show any reduction more than 1 mmHg while for captopril the reduction was marked since 1 hour and reached its maximal at 2 hours. Perindopril seems to be less likely to cause hypotension in patients with heart failure compared to captopril.

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