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Converting enzyme inhibition: Dissociation between antihypertensive and arterial effects

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Summary:

In this study the dose-response curves reflecting the arterial and the antihypertensive effects of converting enzyme inhibition were analysed. The BP measurement (using a random zero sphygmomanometer) and its decrease following converting enzyme inhibition were used as a marker of the arteriolar effect of the drug. The effect on conduit arteries was evaluated through determination of carotid-femoral pulse wave velocity used as an index of arterial distensibility. We compared the dose-response curves of these two parameters in a double-blind study carried out in 24 patients with essential hypertension, who were randomised between placebo and 2, 4 and 8 mg of the converting enzyme inhibitor trandolapril given for 8 days. The antihypertensive effect was observed from 2 mg, at which dose the plateau of BP reduction was already achieved. No significant correlation was found between dose and BP reduction ($r = -0.34$), whereas the dose was significantly related to the change in pulse wave velocity ($r = -0.56$, $P < 0.01$). No significant correlation was found between changes in BP and change of pulse wave velocity. The study provides evidence that the effect on the conduit artery was obtained for higher doses than the BP effect in patients treated for hypertension by the converting enzyme inhibitor trandolapril.

Introduction

Angiotension converting enzyme (ACE) inhibitors lower BP in hypertensive patients through a decrease in peripheral vascular resistance.[1,2] This haemodynamic change represents the principal mechanism of action for the antihypertensive effect of these drugs.[2,3] However, recent studies have shown that ACE inhibitors also affect large arteries causing an increase in arterial diameter and compliance.[4,5] This observation suggests that the interaction between the arterial and BP effects may be difficult to evaluate following antihypertensive drug treatment.[6,7]

The decrease in BP and vascular resistance caused by acute administration of ACE inhibitors is usually characterised by a dose-response curve relating the dose to the pressure or the resistance decrease. This haemodynamic pattern may be considered as a marker of the arteriolar effect of ACE inhibitors.[2,7] On the other hand, studies to evaluate the arterial effect,[4,8] and therefore to establish the dose-response curve on large arteries, are much more difficult to obtain. ACE inhibitors can have a specific relaxing effect on the smooth muscle fibre of the arterial wall thus causing arterial dilatation.[4,8] However, the lowering of BP may by itself have a mechanical effect on arterial diameter, leading to constriction.[4–8] Finally, other nonspecific factors such as those related to the myogenic response and to flow-dependent mechanisms may also influence the arterial changes.[4–9] The combination of all these parameters explains the difficulty in evaluating the direct effect of ACE inhibitors on large arterial vessels. However, when there is a plateau in BP reduction it may be easier to detect a supplementary effect on large arterial vessels. Previous results of a double-blind study versus placebo in healthy volunteers indicated that the arterial effect of the ACE inhibitor perindopril was achieved with higher doses than the effect on BP.[10]

To study this problem we selected the long-acting ACE inhibitor trandolapril.[11–13] From a dose of 1 mg, this compound inhibits ACE in the plasma and decreases BP with a duration of action exceeding 24 hours. In the present design, we investigated the effect of trandolapril at doses of 2, 4 and 8 mg at which similar effects on BP may be expected and thus allowed us to study the effect on conduit arteries.[11–13] This effect on the

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mechanical characteristics of large arteries was investigated from the evaluation of the arterial wall viscoelastic properties, as derived from the determination of carotid-femoral pulse wave velocity.[9,14,15]

Patients and methods

Patients

There were 24 patients with sustained essential hypertension (16 males and 8 females) included in the study. Their age range was between 24 and 61 yrs (mean 47 yrs). Mean ($\pm$ 1SEM) weight and height were 71 $\pm$ 3 kg and 169 $\pm$ 2 cm, respectively. The patients had no signs, symptoms or history of cardiac or renal failure, coronary insufficiency or major diseases other than hypertension. After extensive screening as previously described,[4] all the patients were diagnosed as having essential hypertension. Informed written consent was obtained from each patient after a detailed description of the procedure. The study was approved by INSERM (Institut National de la Santé et de la Recherche Médicale) and the Broussais Hospital Ethical Committee.

Previous treatments, including diuretics, beta-blocking agents or any other antihypertensives drugs, were discontinued at least one month before the study in all patients. Placebo was administered during this ambulatory wash-out period. On the basis of a random zero mercury sphygmomanometer, the 24 patients had a diastolic blood pressure (DBP) $\geqslant$ 95 mmHg at the end of this placebo period. Then patients were randomised in a double-blind design between placebo or 2, 4 and 8 mg once daily of the ACE inhibitor, trandolapril. At these doses, trandolapril inhibits almost all the activity of plasma converting enzyme, as does a dose of 1 mg.[11–13] Trandolapril was given orally at 8 am and continued for 7 days. Haemodynamic investigations were performed just before and at day 7 of treatment, four hours after the last oral administration, i.e. at the maximal BP effect.

Haemodynamic studies were carried out during a one day hospitalisation, at a controlled room temperature of 21 $\pm$ 1°C, the patients having rested for 30 minutes in the recumbent position. Arterial BP and heart rate were measured three consecutive times at the right arm with a random zero mercury sphygmomanometer after one hour of rest and the mean of the three measurements retained for analysis. Phase I of the Korotkoff sounds was used for the determination of SBP and phase V for the evaluation of DBP. The same values of BP were observed in the left and right arms. Mean arterial pressure (MAP) was calculated as the sum of the diastolic pressure plus one-third of pulse pressure.

For determination of the carotid-femoral pulse wave velocity (PWV),[4,9,14,15] two pulse transducer heads (Electronics for Medicine) were fixed to the skin over the most prominent parts of the carotid and femoral arteries. The time delay was measured between the feet of simultaneously recorded pulse waves, with a paper speed of 150 mm/sec. The foot, which contains the high-frequency information, was defined as the point obtained by extrapolating the wave front downward and measured from the intersection of this line with a straight line extrapolation of the last part of the diastolic curve. Measurement of the distance between the two transducers was then used to calculate pulse wave velocity. This was averaged over at least one respiration cycle of about ten cardiac beats.

Statistical methods[16,17]

Statistical analysis was performed with NCSS statistical software (Kaysville, Utah, USA). The nonparametric Kruskal–Wallis method was used to compare means of more than two groups. The Mann–Whitney test was used to compare means of two groups. For correlation analysis, the non-parametric Spearmen rank test was performed; Pearson correlation coefficients lead to the same results and are given in the text. Multiple regression was performed to analyse the pulse wave velocity and BP changes with trandolapril doses. To test if trandolapril lowers BP, the decrease of BP in the placebo group was compared with the three treated groups. The significance level was fixed at $P < 0.05$.

Results

At the beginning of the study, no significant difference between the four subgroups was observed (Table I and II). Following trandolapril, the decrease in SBP, DBP and mean BP was higher in the treated groups than in the placebo group. When the three groups of patients treated with trandolapril were pooled and compared with the placebo subgroup

Table I Clinical characteristics of the patients

	Placebo	*Trandolapril*		
		2 mg	*4 mg*	*8 mg*
Age (yrs)	42 $\pm$ 5	50 $\pm$ 2	49 $\pm$ 4	46 $\pm$ 3
Weight (cm)	64 $\pm$ 4	73 $\pm$ 6	61 $\pm$ 6	79 $\pm$ 3
Body surface area (m^2)	1.78 $\pm$ 0.07	1.83 $\pm$ 0.09	1.65 $\pm$ 0.09	1.97 $\pm$ 0.09

Values are mean $\pm$ 1SEM

Table II Baseline and changes in BP, heart rate and pulse wave velocity

		Placebo	*Trandolapril*		
			2 mg	*4 mg*	*8 mg*
Systolic BP (mmHg)	B	163 ± 6	177 ± 12	162 ± 8	163 ± 5
	C	−8 ± 6	−18 ± 8	−20 ± 7	−25 ± 4
Diastolic BP (mmHg)	B	107 ± 3	113 ± 3	106 ± 3	108 ± 3
	C	−8 ± 5	−9 ± 4	−14 ± 4	−16 ± 3
Mean BP (mmHg)	B	125 ± 2	134 ± 6	126 ± 4	126 ± 4
	C	−8 ± 5	−14 ± 5	−16 ± 5	−19 ± 3
Heart rate (beats/min)	B	59 ± 1	69 ± 2	79 ± 3	68 ± 2
	C	0.1 ± 2.0	−0.3 ± 1.6	−2.8 ± 2.3	−2.2 ± 2.8
Pulse wave velocity (m/sec)	B	12.4 ± 0.9	13.0 ± 1.1	13.7 ± 0.7	12.0 ± 0.9
	C	−0.1 ± 0.4	−0.8 ± 0.5	−2.1 ± 0.7	−1.6 ± 0.4

Values are mean ± 1 SEM
B = baseline values; C = changes after treatment

there was a significant decrease in BP. For SBP, there was a -21 ± 6 mmHg decrease compared with placebo (-8 ± 6 mmHg; $P < 0.05$). Variance analysis did not show any significant statistical difference between the three treated groups (Table II).

Simple correlation study

When trandolapril doses was expressed in mg, there was (Figure 1) a significant and negative correlation between the dose and the pulse wave velocity changes ($r = -0.43$, $P < 0.05$), whereas no significant correlation was observed between the dose and changes in SBP ($r = -0.31$) or DBP ($r = -0.31$).

When trandolapril dose was expressed in mg/kg, similar results were noted. Figure 1 shows the significant correlation between the dose (mg/kg) and the pulse wave velocity changes ($r = -0.56$, $P < 0.01$). No significant correlation was observed between the dose and changes in SBP ($r = -0.37$) or DBP ($r = -0.34$).

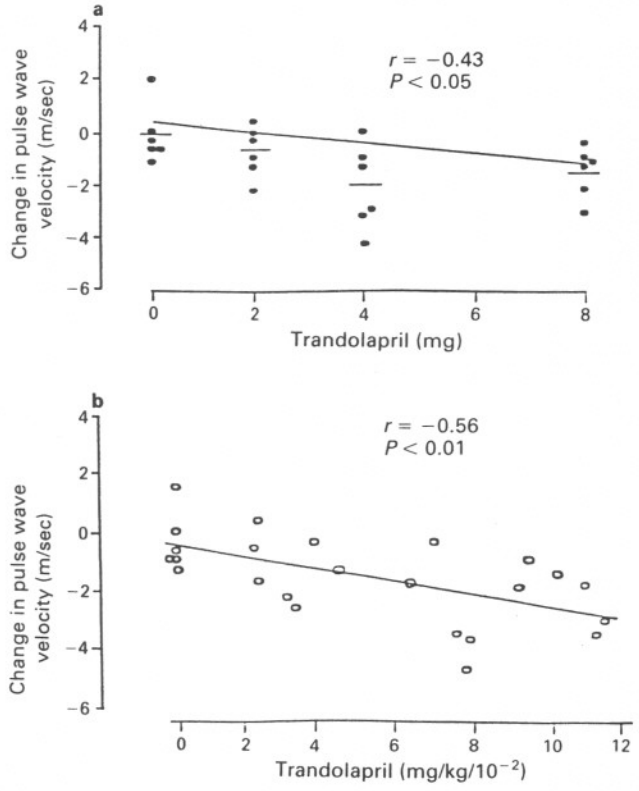

Figure 1 Relationship between changes in pulse wave velocity and doses of trandolapril. Absolute trandolapril doses per mg (a) and (b) trandolapril doses per weight (mg/kg/10^{-2}).

Multiple regression analysis

The analysis of the change in pulse wave velocity by multiple regression (change in BP and dose of trandolapril) confirm these results (Table III).

When the dose of trandolapril is expressed in milligrams there was a significant correlation between the change in pulse wave velocity and dose of trandolapril even after adjustment of SBP ($r = -0.47$, $P = 0.01$) or DBP changes ($r = -0.46$, $P < 0.05$). No significant correlation was noted between pulse wave velocity and BP changes after adjustment of doses.

Similar results were noted when trandolapril dose was expressed in mg/kg with a significant

Table III Linear correlation coefficients between trandolapril doses expressed in mg or mg/kg and the pulse wave velocity changes adjusted to SBP or DBP changes. $n = 24$, total population; $n = 18$, placebo group is excluded

	Pulse wave velocity changes (adjusted to BP reduction)	
	SBP	DBP
n = 24 patients		
Trandolapril (mg)	$r = -0.47$**	$r = -0.46$*
Trandolapril (mg/kg)	$r = -0.56$***	$r = -0.58$***
n = 18 patients		
Trandolapril (mg)	$r = -0.35$(NS)	$r = -0.33$(NS)
Trandolapril (mg/kg)	$r = -0.54$*	$r = -0.49$*

*$P < 0.05$ **$P < 0.01$ ***$P < 0.001$

correlation between the pulse wave velocity changes and dose of trandolapril adjusted to changes in SBP ($r = -0.56$, $P < 0.001$) or DBP ($r = -0.58$, $P < 0.001$). No significant correlation was observed between pulse wave velocity changes and BP.

Discussion

In the present double-blind randomised study versus placebo, the antihypertensive effect of trandolapril clearly appeared when the three subgroups (2, 4 and 8 mg) were pooled and compared with the placebo group. The finding agrees with previous observations showing that trandolapril decreases BP at the 1 mg dose with almost a maximal (plateau) effect at 2 mg.[11–13]

One of the principal findings of the study was that no significant difference in BP decrease was observed between the 2, 4 and 8 mg doses. This result was confirmed by the lack of significant correlation between trandolapril dose and the decrease in BP, suggesting that maximal BP reduction was indeed obtained from 2 mg. Therefore, the present design provided an adequate evaluation of the status of large arteries following ACE inhibition. Indeed, previous results in our laboratory indicated that the higher the BP reduction the higher its mechanical effect and the lower the increase in brachial arterial diameter following ACE inhibition.[18] Thus, using the present design any arterial modifications due to ACE inhibition were presumably not dependent on the BP reduction itself.

The arterial effect of trandolapril was investigated from the determination of carotid-femoral pulse wave velocity. Whereas BP reduction did not correlate with trandolapril dose, pulse wave velocity was significantly correlated with the dose of the ACE inhibitor. Thus, the higher the dosage the lower the pulse wave velocity and therefore the higher the distensibility in the aortic circulation. As no significant correlation was observed between the change in BP and the change in pulse wave velocity, it appears that the improvement in aortic distensibility was a drug-mediated effect and not only a pressure-mediated effect, as was previously shown with other ACE inhibitors in various clinical and experimental situations.[4,19,20] In a recent study in hypertensive subjects,[21] we showed that intravenous perindoprilat given at two doses (1 and 2.5 μg/kg/min) caused a similar BP reduction but brachial artery diameter increased only for the higher doses. At the same time a complete disappearance of ACE was observed in the plasma and it seemed likely that the conduit artery effect was related to change in the renin-angiotensin system within the vascular tissue.[6,21] In the present study, this interpretation agrees with the predominant local effect of trandolapril and its long duration of action.[11–13]

In conclusion, our study strongly suggests that in the systemic circulation the dose of ACE inhibitor producing arterial changes and BP effects may be dissociated, and that ACE inhibition at high doses can have specific consequences for arterial stiffness. Owing to the small number of patients in the present study, it will be interesting to confirm this conclusion in a larger population on long-term treatment.

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