Are prostaglandins involved in the antihypertensive effect of dihydralazine?

INGRID W. REIMANN, D. RATGE,* H. WISSEr AND J. C. FRÖLICH
Dr Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, and *Robert-Bosch-Krankenhaus, Stuttgart, FRG

Summary

1. Two female and two male patients with essential hypertension were given dihydralazine plus saline or dihydralazine plus diclofenac intravenously on two separate occasions. The dihydralazine dose (range: 16.2-32.4 mg/2 h) was chosen individually to reduce systolic blood pressure by 20 mmHg from the control value before the investigation; the intravenous diclofenac dose was 75 mg/20 ml of saline for all patients.

2. Dihydralazine decreased diastolic blood pressure more than systolic blood pressure and increased heart rate; diclofenac reduced both of these effects.

3. Dihydralazine increased urinary volume and sodium clearance; both these effects were antagonized by concomitant treatment with diclofenac.

4. Whereas dihydralazine did not influence creatinine clearance appreciably, concomitant administration of diclofenac reduced creatinine clearance.

5. Urinary prostaglandin E₂ was reduced by diclofenac.

6. We suggest that dihydralazine-mediated vasodilatation is reduced by cyclo-oxygenase inhibition.

Key words: diclofenac, dihydralazine, prostaglandins, vasodilatation.

Introduction

Dihydralazine is a widely used antihypertensive agent which acts by relaxing the smooth muscles of precapillary arterioles and thus decreases peripheral arteriolar resistance [1]. The molecular mechanism of action of dihydralazine is not well understood at present. Prostaglandins (PG) are known to participate in the regulation of vascular reactivity and blood pressure. They may interfere by opposing the vasoconstrictor and antinatriuretic actions of the renin-angiotensin-aldosterone system [2, 3], by modulating the action and/or release of noradrenaline from vasoconstrictor nerves [4], by amplifying the effects of the kallikrein-kinin system [5] or by acting directly on vascular smooth muscles [6]. The vasodilator PG (PGE₂, PGI₂, PGD₂) could act locally although it has been suggested that circulatory PGI₂ has a role as it (in contrast to the other PG) is not inactivated on passage through the pulmonary vascular bed [7].

It is possible that vasodilator PG could play a role in the action of dihydralazine. We have investigated their contribution by comparing the effects of dihydralazine before, and after, blockade of cyclo-oxygenase, the enzyme essential for PG synthesis. The study was carried out as an acute experiment, infusing both dihydralazine and the cyclo-oxygenase inhibitor diclofenac in order to avoid interference by sodium retention, a known effect of cyclo-oxygenase inhibitors given chronically.

Patients and methods

Patients

Four patients, two females and two males, aged 23, 40, 30 and 56 years, participated in this pilot study and gave written informed consent. All of them had had mild to moderate essential hypertension for 2–7 years, blood pressure values ranging from 160/110 to 210/130 mmHg, but were otherwise healthy and had normal renal function.

The patients were withdrawn from treatment in
hospital and brought into sodium balance on 150 mmol of sodium/day. They all became normo-
tensive with respect to systolic blood pressure; two patients had slightly elevated diastolic blood
pressure values at the start of the study.

**Study design**

After having come into sodium balance the intravenous dose of dihydralazine required to
reduce supine systolic blood pressure by 20 mmHg from control was determined for each
individual in a pilot study several days before the acute treatment was started. In this initial study a
solution containing 150 mg of dihydralazine as methanesulphonate (Nepresol, Ciba-Geigy) in
50 ml of saline was infused at rates of 2.7, 5.4, 8.1, 10.8 and 16.2 mg/h with an infusion pump.
The infusion rates were increased in 30 min intervals. Blood pressure (method of Riva-Rocci,
discontinuously) and pulse rate controls were done in 5–10 min intervals.

The acute study was performed in all patients according to the same regimen lasting from 07.00
hours to noon, in single-blind, randomized crossover fashion, with a 1 day interval between the 2
days of acute treatment.

At 09.00 hours indwelling catheters were placed into the cubital veins in both arms. A dose
(75 mg) of diclofenac (Voltaren, Geigy), in 20 ml of saline, or placebo (saline) was injected 1 h
before starting the infusion of dihydralazine, the individual, previously determined dose being
used. Blood samples for determination of sodium, potassium and creatinine were taken 1 h after-
wards by venepuncture from the forearm vein contralateral to the infused vein. At 10.00 hours a
2 h dihydralazine infusion was started, the infusion rates varying from individual to indi-
vidual (between 0.045 and 0.090 ml/min). Blood samples for determination of the above-mentioned
parameters were drawn at 30 min intervals during the infusion. Urine samples for determination of
sodium, potassium, creatinine and PGE₂ were
collected during the 2 h interval before the study
(07.00–09.00 hours) and the 3 h interval (09.00
hours to noon) during the experiment.

**Analyses**

Sodium and potassium in plasma and urine were measured by flame photometry and
creatinine by the Jaffé reaction with picric acid. Urinary PGE₂ values were determined by pre-
viously published methods [8; I. W. Reimann & J. C. Frolich, unpublished work].

**Results**

The results of this study are summarized in Table 1; because of the small number of patients no
statistical data are given.

As can be seen from Table 1 the dihydral-
azine-induced effects on diastolic blood pressure
heart rate, urine excretion rate and sodium
clearance are impressively reduced, coincident
with a marked depression in urinary PGE₂
excretion rate, which reflects an inhibition of
The systolic blood pressure reduction by
dihydralazine was less during the acute study
compared with the pilot study, where a mean of
-20 mmHg was attained. The influence of
diclofenac on dihydralazine-induced reduction of
systolic blood pressure is only a slight one.
Urinary potassium output was not changed by
either dihydralazine or by concomitant treat-
mant with diclofenac.

**Discussion**

This study shows that the blood pressure-
lowering effect of dihydralazine was attenuated
by diclofenac. The effect was most clearly visible
with respect to the diastolic values; systolic
values were less affected. The increase in heart
rate by dihydralazine was also attenuated by
diclofenac. Urinary PGE₂ tended to increase with

<table>
<thead>
<tr>
<th>Table 1. Effect of dihydralazine on cardiovascular and renal function before and after diclofenac administration in four patients with essential hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Urine volume (ml/min)</td>
</tr>
<tr>
<td>C_Creatinine (ml/min)</td>
</tr>
<tr>
<td>Urinary PGE₂ (pg/min)</td>
</tr>
</tbody>
</table>

Means ± SEM are shown.

320s
dihydralazine whereas diclofenac caused 60% reduction.

The dihydralazine-induced changes in renal function (increases in urine flow rate and sodium clearance) are coincident with the renal effects of vasodilating PG and they were fully antagonized by concomitant treatment with the PG inhibitor diclofenac.

There are several ways by which PG could mediate the cardiovascular action of dihydralazine. Stimulation of PG biosynthesis would lead to increased amounts of locally acting or circulating vasodilator PG, which may cause a direct relaxation of vascular smooth muscles [6] or may amplify the vasodilating properties of the kallikrein-kinin system [5]. A further important mechanism could be modulation of sympathetic reflex activation. Hedqvist and co-workers have pointed out that PG might exert a prejunctional action on adrenergic neurotransmission; for example, PGE₂ inhibits vasoconstriction responses to nerve stimulation by inhibition of noradrenaline release [4]. On the other hand PG₁ had no effect on neurally induced transmitter release; its modulation of vasoconstrictor responses, at least to renal nerve stimulation, was interpreted as a postjunctional phenomenon [4]. Taken together, locally formed vasodilating PG could modulate adrenergic neuroeffector transmission by a negative feedback mechanism [10] in which pre- and post-junctional actions may be involved.

Renal renin release is regulated by cyclooxygenase-dependent mechanisms [2] as well as via the renal nerves and circulating catecholamines by both β- and α-adrenoceptors [for reviews see 2, 11]. Enhancement of renin release after dihydralazine administration is a well-known effect, attributed to increased reflex sympathetic activity [12], but perhaps mediated by direct PG-dependent stimulation as well.

Investigations by Haeusler & Gerold [13] demonstrated increased levels of prostaglandin-like material in the blood of dogs during arterial hypotension induced by dihydralazine and Förster and co-workers [14] were able to show enhanced PG₁₂ biosynthesis in the aortas of spontaneously hypertensive rats after dihydralazine administration.

The results of the present study differ from those recently described by Campbell et al. [15], who investigated the effects of indomethacin on hydralazine-induced renal and catecholamine release in conscious rabbits. Even though indomethacin inhibited renal venous PGE₂ production by 56%, as well as hydralazine-induced tachycardia and increase in plasma renin activity by 24% and 75% respectively, it failed to alter significantly hydralazine-induced increases of plasma catecholamines. The hypotensive effect of hydralazine was augmented by 6%. These differences, besides pointing to species variation, show that several factors important for the regulation of blood pressure are affected by prostaglandin inhibition.

Acknowledgments
This study was supported by the Robert-Bosch-Foundation, Stuttgart, Germany (FRG). We acknowledge the expert assistance of Mrs E. Golbs. Mrs I. Koch kindly prepared the manuscript.

References