Prostaglandin E$_2$ Analogue Elicits Renal and Hormonal Compensatory Mechanisms in Human Hypertension

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SUMMARY  Endogenous prostaglandin E$_2$ appears to play an important role in cardiovascular homeostasis. When administered exogenously, it is a potent vasodilator, but the requirement for intravenous administration and its short duration of action have limited studies to its acute effects. A novel prostaglandin E$_2$ analogue, CL115347, can be administered transdermally on a long-term basis. The cardiovascular responses to the chronic administration of CL115347 were studied in a double-blind, placebo-controlled trial in 26 subjects with essential hypertension (16 given drug, 10 placebo) maintained on a 100-mEq sodium diet. Administration of CL 115347 produced a fall in diastolic blood pressure of 7.8 ± 1.3 mm Hg, compared with a 2.3 ± 1.7 mm Hg fall in controls (p = 0.02), with no change in heart rate. The direct vascular effect of the drug was confirmed by attenuation of the vasoconstrictor response to angiotensin II infusion (13.4 ± 3.1 vs 21 ± 2 mm Hg at 3.0 ng/kg/min; p < 0.05). However, the chronic blood pressure effect of CL 115347 was modest. Subjects receiving active drug showed significant compensatory increases in plasma renin, aldosterone, and norepinephrine levels accompanied by sodium retention and kaliuresis. In summary, chronic administration of this prostaglandin E$_2$ analogue resulted in a modest decrease in blood pressure and antagonism of angiotensin II-mediated vasoconstriction. However, its effects were largely offset by compensatory increases in vasoconstrictor hormones and sodium retention. (Hypertension 8: 489-496, 1986)

KEY WORDS  • blood pressure • renin-angiotensin system • catecholamines • sodium retention

ARTERIAL blood pressure is dependent on several factors, including the balance between vasoconstrictor and vasodilator substances. It has been postulated that deficient production of vasodilator hormones such as endogenous prostaglandin E$_2$ (PGE$_2$) may underlie the pathogenesis of some patients with essential hypertension.1,2 Prostaglandin E$_2$ is produced locally in the kidney, where it increases renal blood flow and induces natriuresis, and in the vasculature, where it produces vasodilatation and reduces the pressor response to angiotensin II (ANG II).3,4 In addition, PGE$_2$ inhibits norepinephrine (NE) release from peripheral nerve endings.5 Although PGE$_2$ is an effective hypotensive agent in humans, it must be given intravenously and has a brief duration of action. Thus, the chronic cardiovascular effects of PGE$_2$ in humans have not been studied previously.

CL 115347 is the methyl ester of (±)-15-deoxy-16-hydroxy-16(α/β)-vinyl PGE$_2$ (Figure 1). In animal models of hypertension it has been shown to be 100 to 250 times more potent than PGE$_2$ as an antihypertensive, with a prolonged duration of action.6 It is active when administered orally, intravenously, or transdermally. The availability of this PGE$_2$ analogue enabled us to examine the cardiovascular, renal, and hormonal response to the chronic administration of PGE$_2$ to humans with essential hypertension.
overnight fast on the day before randomization and ed subjects four times daily (0800, 1200, 1600, 2200). These studies, except for radiography, were repeated (PRA) was measured with the subjects supine and after pertrophy, were grounds for dismissal from the study. Other than findings consistent with left ventricular hypotension, diabetes mellitus, coronary artery disease, or other cardiovascular diseases were excluded. The same double-blind protocol was followed at least 2 weeks before admission. Subjects with secondary hypertension, diabetes mellitus, coronary artery disease, or other cardiovascular diseases were excluded. The same double-blind protocol was followed at all three institutions and was approved by the respective human subjects committees. All participants gave informed consent. On admission to the hospital, subjects were placed on an isocaloric diet containing 100 mEq sodium, 70 mEq potassium, and 400 mEq calcium and underwent complete histories and physical examinations. An extensive laboratory evaluation, including full chemistry profile, complete blood count with differential, Westergren sedimentation rate, bleeding time, and urinalysis, and electrocardiography and chest radiography were also performed. Marked abnormalities in any of the results (greater than the upper limits of normal), other than findings consistent with left ventricular hypertrophy, were grounds for dismissal from the study. These studies, except for radiography, were repeated at intervals throughout the admission.

Subjects and Methods
Twenty-six hypertensive subjects (23 men, 3 women), aged 18 to 60 years (mean, 38.8 ± 2.5 years), were prospectively studied in three locations: Boston (9 subjects), New Haven (7 subjects), and Miami (10 subjects). All had supine, sitting, and standing diastolic blood pressures of 95 to 114 mm Hg determined at least three times during each of three separate office visits. None of the subjects had received any antihypertensive agents or prostaglandin inhibitors for at least 2 weeks before admission. Subjects with secondary hypertension, diabetes mellitus, coronary artery disease, or other cardiovascular diseases were excluded. The same double-blind protocol was followed at all three institutions and was approved by the respective human subjects committees. All participants gave informed consent.

On admission to the hospital, subjects were placed on an isocaloric diet containing 100 mEq sodium, 70 mEq potassium, and 400 mEq calcium and underwent complete histories and physical examinations. An extensive laboratory evaluation, including full chemistry profile, complete blood count with differential, Westergren sedimentation rate, bleeding time, and urinalysis, and electrocardiography and chest radiography were also performed. Marked abnormalities in any of the results (greater than the upper limits of normal), other than findings consistent with left ventricular hypertrophy, were grounds for dismissal from the study. These studies, except for radiography, were repeated at intervals throughout the admission.

Data Collection
Pulse rate and blood pressure were recorded in seated subjects four times daily (0800, 1200, 1600, 2200). Daily weights were obtained. Plasma renin activity (PRA) was measured with the subjects supine and after 2 to 4 hours of ambulation in the morning following an overnight fast on the day before randomization and while receiving the study drug. Electrolyte balance and creatinine clearances were assessed daily after collection of 24-hour urine specimens.

Study Design
Following a 4-day run-in period in which baseline data collection was performed and metabolic balance was obtained, the subjects were randomized to receive either placebo or CL 115347 (Lederle Laboratories, Pearl River, NY, USA). Randomization was performed at Lederle Laboratories; 60% of subjects received CL 115347 and 40% received placebo. The agent (drug or placebo) was supplied in the form of an ointment-containing syringe prefilled by the pharmaceutical company. This agent was spread onto a raised, demarcated area of a plastic template, which was then applied to alternating sites on the volar aspect of the forearm at 12-hour intervals (0800 and 2000). Daily doses ranged from 1000 to 3000 µg. Two subjects required dosage reductions due to transient side effects (see Results). All subjects randomized at the completion of the run-in period completed the study.

Additional studies were performed in Boston (9 subjects: 5 given drug, 4 placebo) to assess any compensatory or secondary hormonal responses, changes in renal hemodynamics, or pressor responsivity to drug or placebo. Thus, at 0700 on the third day of the run-in period, following an overnight fast, an intravenous catheter was placed in an arm vein with the subject still supine. At 0800, baseline blood samples were drawn for measurement of PRA, aldosterone, cortisol, NE, and epinephrine. The subjects were then ambulated for 2 hours, after which blood samples again were drawn. The subjects ate breakfast, returned to recumbency, and had a second intravenous line placed in the contralateral forearm. After a further 45 to 60 minutes, baseline blood samples again were drawn for measurement of PRA, aldosterone, NE, epinephrine, cortisol, sodium, potassium, p-aminohippurate (PAH), and inulin. Loading doses of PAH (8 mg/kg) and inulin (50 mg/kg) were administered, followed by continuous infusion (PAH, 12 mg/min; inulin, 30 mg/min) through an infusion pump (IMED, San Diego, CA, USA). After 60 minutes, the baseline blood sampling was repeated and ANG II infusion (Hypertensin; Ciba Geigy, Summit, NJ, USA) was begun at a rate of 0.3 ng/kg/min using a Harvard pump (Millis, MA, USA). Blood pressure was recorded at 2- and 10-minute intervals (Roche Arteriosonde, Nutley, NJ, USA). After 45 minutes, blood sampling was repeated and the ANG II infusion rate was increased to 1.0 ng/kg/min. Blood samples were again drawn after 45 minutes, and the infusion rate was increased to 3.0 ng/kg/min. Following the drawing of blood samples at this dosage, the infusion was terminated and the intravenous catheters removed. On the next day, subjects received NE infusion, which was begun at a rate of 10 ng/kg/min and increased to 30 ng/kg/min over 10 to 20 minutes. Blood pressure was recorded at 2-minute intervals as already described.

The same posture study and ANG II and NE infu-
sions were repeated on the fifth and sixth day of drug (or placebo) administration.

**Laboratory Procedures**

All blood samples were collected on ice and spun immediately, and the plasma was separated and frozen until assay. Samples for PRA were drawn with ethylenediaminetetraacetic acid as the anticoagulant. Heparin was the anticoagulant in samples for aldosterone and cortisol. Aldosterone, cortisol, and PRA were measured with previously described radioimmunoassay methods. Plasma catecholamines were determined by the modified radioenzymatic method of Peuler and Johnson. Serum and urine sodium and potassium were measured by flame photometry using lithium as the internal standard. Plasma PAH was measured with a Technicon autoanalyzer (Tarrytown, NY, USA).

**Statistical Analysis**

Results are presented as group means ± standard error of the mean (SEM). Blood pressure results were assessed by analysis of variance with sources of variance extracted for investigator, treatment, and treatment by investigator. Hormonal responses were tested with the Wilcoxon rank-sum test. The null hypothesis was rejected when $p$ achieved a value of 0.05 or less.

**Results**

All 26 subjects who were prospectively randomized completed the double-blind study. Subject characteristics are shown in Table 1. There were no significant differences in the groups with respect to sex, race, age, weight, or blood pressure on randomization. Four subjects were excluded before randomization during the run-in period for failure to maintain diastolic pressure greater than 90 mm Hg (2 subjects), marked abnormalities in blood test results on admission (1 subject), or accidental loss of blinding due to nursing error (1 subject).

Baseline blood pressures (final day of run-in period) were the same in drug-treated and placebo-treated groups (Figure 2; see Table 1). With treatment, the group receiving CL 115347 had a prompt decline in blood pressure. By the second day, the mean sitting systolic pressures for the drug-treated group had declined 7.7 ± 2.2 mm Hg as compared to their own predrug baseline values ($p < 0.01$); sitting diastolic pressure decreased similarly by 8.2 ± 1.4 mm Hg ($p < 0.01$). No significant change was seen in the placebo-treated group (see Figure 2). The blood pressure remained at approximately this level for the drug-treated group throughout the trial. After the second day, the between-group difference became smaller. For the 7 days of treatment, the subjects receiving CL 115347 exhibited an average fall in systolic pressure of 7.4 ± 1.7 mm Hg from predrug levels and 5.8 mm Hg when compared with that in placebo-treated controls ($p = 0.1$), as well as an average fall in diastolic pressure of 7.8 ± 1.3 mm Hg from predrug baseline levels and 5.4 mm Hg when compared with that in placebo-treated controls ($p = 0.02$). Of note, despite a CL 115347 dosage range of 1000 to 3000 μg, no dose-response relationship was seen. The magnitude of hypotensive effect was similar at all three centers. Heart rate was the same in treatment and control groups at baseline and did not change during the study (see Figure 2).

Supine and upright PRA levels are available for 22 subjects (10 given placebo, 12 drug). The remaining four subjects had incomplete data and were excluded from analysis. As can be seen in Figure 3, supine PRA
rose from baseline in response to CL 115347 treatment (from 1.77 ± 0.7 to 2.51 ± 0.7 ng angiotensin I/ml/min; \( p < 0.05 \)), while subjects receiving placebo showed no significant change (from 1.42 ± 0.4 to 0.88 ± 0.26 ng angiotensin I/ml/min). In response to upright posture, there was a clear trend toward an increase in PRA in subjects receiving active drug, although the overall change was not significantly different from that seen in the placebo-treated group.

Plasma aldosterone levels followed the trend seen with PRA: a significant difference was noted in the supine plasma aldosterone levels in the subjects receiving CL 115347 as compared with that seen in placebo-treated subjects (Table 2). These changes could not be explained by adrenocorticotropic hormone–induced stimulation of aldosterone release because plasma cortisol levels were not different between groups or test periods (see Table 2). Supine epinephrine levels did not change (see Table 2), nor did the epinephrine response to posture (data not shown). As shown in Figure 4, however, plasma NE levels rose in the group receiving CL 115347. During the run-in period, supine NE levels in the drug-treated group exceeded those in the placebo-treated group (268 ± 123 vs 171 ± 32 pg/ml). The apparent difference was due entirely to one subject. By Day 5 of treatment, plasma NE levels were significantly different between drug-treated and placebo-treated groups (235 ± 15 vs 123 ± 22 pg/ml; \( p = 0.014 \)). In response to upright posture, plasma NE levels were not significantly different from baseline (354 ± 28 vs 292 ± 34 pg/ml at 5 minutes; 268 ± 70 vs 274 ± 37 pg/ml at 2 hours). On Day 5, plasma NE levels in response to upright posture were significantly higher in the drug-treated group at 5 minutes (440 ± 103 vs 263 ± 36 pg/ml; \( p = 0.029 \)) and at 2 hours (509 ± 105 vs 280 ± 35 pg/ml, \( p = 0.029 \)).

Pressor responsiveness was assessed with infusions of ANG II. The blood pressure response to ANG II was

<table>
<thead>
<tr>
<th>Variable</th>
<th>Run-in (Day -2)</th>
<th>Study (Day +5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 4)</td>
<td>CL 115347 (n = 5)</td>
</tr>
<tr>
<td>PRA (ng ANG I/ml/min)</td>
<td>1.42 ± 0.4</td>
<td>1.77 ± 0.7</td>
</tr>
<tr>
<td>Aldosterone (ng/ml)</td>
<td>16.6 ± 2.7</td>
<td>16.0 ± 3.9</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>171.3 ± 32</td>
<td>267.7 ± 123</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>50.8 ± 20</td>
<td>46.7 ± 27</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>10.0 ± 1.3</td>
<td>11.5 ± 1.6</td>
</tr>
<tr>
<td>Sodium (mEq/dl)</td>
<td>141.0 ± 0.7</td>
<td>139.2 ± 1.3</td>
</tr>
<tr>
<td>Potassium (mEq/dl)</td>
<td>4.3 ± 0.8</td>
<td>4.2 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means ± SEM. All blood samples were drawn in supine, fasting subjects at 0800. Both groups received placebo during the run-in period.

PRA = plasma renin activity; ANG I = angiotensin I.

*p < 0.05, compared with values in placebo-treated group.
PROSTAGLANDIN ANALOGUE IN HUMAN HYPERTENSION/Given et al. 493

Figure 5. Effect of CL 115347 (n = 5) or placebo (n = 4) on the pressor response to angiotensin II infusion. Both groups received placebo during the run-in period. Asterisk indicates a significant difference (p < 0.05) between groups.

Although inulin clearances did not change between the run-in and study periods for either group (Table 4), sodium retention (as documented by 24-hour urinary sodium excretion) was noted in both groups (cumulative sodium balance by Day 7 was + 95.7 ± 34 mEq for drug-treated group and + 14.7 ± 57 mEq for the placebo-treated group). Sodium retention was accompanied by kaliuresis in drug-treated subjects (Figure 6). Systemic infusion of ANG II (up to 3 ng/kg/min) attenuated by CL 115347. As can be seen in Figure 5, at infusion rates of 0.3, 1.0, and 3.0 ng/kg/min, there were no differences between drug-treated and placebo-treated groups before randomization. During therapy, however, the subjects receiving CL 115347 became less responsive. This trend was first apparent at the 1.0 ng/kg/min dose (drug vs placebo treatment: 7.6 ± 1.9 vs 10.8 ± 0.9 mm Hg) and became significant at the maximum dose of 3.0 ng/kg/min (13.4 ± 3.1 vs 21 ± 2.0 mm Hg; p = 0.032). This CL 115347-induced attenuation in pressor response appeared to be specific for ANG II since it did not influence the pressor effect of NE infusion (Table 3).

Table 3. Maximal Pressor Response to Norepinephrine Infusion (30 ng/kg/min) in Hypertensive Subjects Receiving Either Placebo or CL 115347

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Placebo (n = 4)</th>
<th>CL 115347 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run-in</td>
<td>Study</td>
</tr>
<tr>
<td>Systolic</td>
<td>+ 9 ± 3.5</td>
<td>+ 7.5 ± 0.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>+ 9 ± 2.7</td>
<td>+ 6.5 ± 1.3</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

Table 4. Inulin and p-Aminohippurate Clearance During Angiotensin II Infusion (ml/min) in Hypertensive Subjects Receiving Either Placebo or CL 115347

<table>
<thead>
<tr>
<th>ANG II infusion (ng/kg/min)</th>
<th>Placebo (n = 4)</th>
<th>CL 115347 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run-in</td>
<td>Study</td>
</tr>
<tr>
<td>Inulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>130 ± 13</td>
<td>119 ± 11</td>
</tr>
<tr>
<td>0.3</td>
<td>132 ± 13</td>
<td>123 ± 12</td>
</tr>
<tr>
<td>1.0</td>
<td>134 ± 11</td>
<td>126 ± 13</td>
</tr>
<tr>
<td>3.0</td>
<td>133 ± 11</td>
<td>124 ± 19</td>
</tr>
<tr>
<td>PAH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>621 ± 50</td>
<td>652 ± 70</td>
</tr>
<tr>
<td>0.3</td>
<td>627 ± 62</td>
<td>625 ± 52</td>
</tr>
<tr>
<td>1.0</td>
<td>540 ± 36</td>
<td>592 ± 55</td>
</tr>
<tr>
<td>3.0</td>
<td>510 ± 30</td>
<td>543 ± 45</td>
</tr>
</tbody>
</table>

Values are means ± SEM. ANG II = angiotensin II; PAH = p-aminohippurate.
did not influence inulin clearances in either group during either period (see Table 4).

Clearance of PAH, a measure of renal plasma flow, showed a small, nonsignificant downward trend for subjects receiving CL 115347 after 5 days of therapy (from 618 ± 60 to 571 ± 40 ml/min; see Table 4). Infusion of ANG II resulted in a decline in PAH clearances during the run-in periods for both groups. During the study period, CL 115347 administration attenuated the ANG II–induced decline in PAH clearance, but this effect was not statistically significant. We examined the influence of CL 115347 on renal vascular resistance, which was estimated as (mean blood pressure/PAH clearance) × 80 (expressed as × 10^3 dyn·sec·cm⁻¹). There was no significant difference between groups at baseline. Treatment with CL 115347 did not significantly alter basal renal vascular resistance, which was 14.4 ± 2.4 and 14.4 ± 1.6 × 10^3 dyn·sec·cm⁻¹ during the run-in and study periods, respectively, for the placebo-treated group and 14.4 ± 1.6 and 15.2 ± 1.6 × 10^3 dyn·sec·cm⁻¹ during these periods for the drug-treated group. However, a decline in the renal vasoconstrictor response to ANG II infusion was observed (Table 5). During the 3.0-ng/kg/min ANG II infusion dose, the difference in renal vascular resistances between run-in and study periods in the drug-treated, but not the placebo-treated, group was significant (p < 0.01).

Minor side effects were common and related predominately to local vasodilatation at the application site (Table 6). These side effects were considered mild by the subjects and did not lead to discontinuation of treatment. Three subjects reported myalgias, and one required a dosage reduction from 3000 to 1000 µg/day. The drug was stopped for 12 hours, then restarted at a maximum dose of 2000 µg/day without recurrence of rash. A transient flulike syndrome with abdominal cramping and diarrhea developed in a subject receiving 3000 µg/day acquired a blotchy, macular rash. The drug was stopped for 12 hours, then restarted at a maximum dose of 2000 µg/day without recurrence of rash. A transient flulike syndrome with abdominal cramping and diarrhea developed in a subject receiving 3000 µg/day. However, this condition resolved spontaneously without a decrease in drug dosage, its relationship to CL 115347 was doubtful. One subject experienced a transient decrease in white blood cell count, from 6.0 to 1.9 × 10^9/ml, the cause of which was unclear. This condition resolved spontaneously without discontinuation of the drug. Several subjects receiving CL 115347 experienced prolongation of bleeding times, which in three were outside the normal range. Bleeding times in other subjects decreased or were stable. Overall there was no change for the drug-treated group when compared with baseline values or values in placebo-treated subjects (Table 7). No episodes of clinical bleeding occurred. One patient receiving placebo experienced myalgia. No other complications were reported in subjects receiving placebo.

**Discussion**

The present study was designed to evaluate the cardiovascular, renal, and endocrine effects of chronic PGE₂ analogue administration in humans. To our knowledge, this is the first such study. Previous studies on the acute administration of PGE₂ to normotensive humans reported decreases in blood pressure of 10 to 34% that were accompanied by increases in heart rate of 20 to 40%. 11-14 As shown in Figure 2, the effect of CL 115347 on diastolic blood pressure was modest but sustained. There was no change in heart rate. This response was not dose-dependent over the narrow range of dosages studied.

Our study demonstrates that chronic administration of PGE₂ analogue resulted in a modest blood pressure effect but stimulated a number of renal and hormonal responses that offset the vasodilator effects of the drug. As shown in Figure 3, PRA in the drug-treated group

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**Table 5. Percentage Change in Renal Vascular Resistance (× 10^3 dyn·sec·cm⁻¹) as Compared to Baseline During Angiotensin II Infusion in Hypertensive Subjects Receiving Either Placebo or CL 115347**

<table>
<thead>
<tr>
<th>ANG II infusion (ng/kg/min)</th>
<th>Placebo (n = 4)</th>
<th>CL 115347 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run-in</td>
<td>Study</td>
</tr>
<tr>
<td>0.3</td>
<td>+ 10.4 ± 5</td>
<td>+ 8.6 ± 1.4</td>
</tr>
<tr>
<td>1.0</td>
<td>+ 35.4 ± 13</td>
<td>+ 26.2 ± 1.9</td>
</tr>
<tr>
<td>3.0</td>
<td>+ 55.3 ± 18</td>
<td>+ 51.7 ± 4.5</td>
</tr>
</tbody>
</table>

Values are means ± SEM. ANG II = angiotensin II.

*p < 0.01, compared with corresponding run-in period.
rose 42%, as compared with that seen during the run-in period, and 285% in placebo-treated controls, as compared with that seen during the study period ($p < 0.05$). This increase in PRA could result from direct stimulation of renin release by the PGE\textsubscript{2} analogue or an indirect response to hypotension, or both. The relationship between the increase in PRA and PGE\textsubscript{2} activity has been supported by the observation that administration of the prostaglandin synthetase inhibitor indomethacin to sodium-depleted hypertensive humans blocked the rise in PRA.\textsuperscript{15} Whatever the mechanism, the increase in PRA was accompanied by maintenance of an elevated aldosterone level in the group receiving active drug for 5 days ($p < 0.05$). Interestingly, CL 115347 did not influence the pressor response to exogenous noradrenaline, suggesting a somewhat specific effect on ANG II–mediated vasoconstriction. Inulin and PAH clearances also were performed during ANG II infusion, as shown in Table 4. Administration of CL 115347 appeared to attenuate the fall in renal plasma flow (as measured by PAH) in response to ANG II. Inulin clearance, representing glomerular filtration rate, did not change in either group. Thus, CL 115347 reduced vascular responsiveness to infused ANG II in the peripheral circulation, including the renal vasculature.

As stated earlier, previous studies have demonstrated that PGE\textsubscript{2} infusion can result in tachycardia. This response has been attributed to a direct chronotropic effect\textsuperscript{6-13} or, alternatively, considered a baroreceptor reflex response to hypotension.\textsuperscript{11,12} Our subjects did not manifest tachycardia at any time during this study. Animal studies with CL 115347 revealed only modest
increases in heart rate (5–10%) and showed no direct positive chronotropic effects. We interpret these findings to indicate that unlike PGE₂, CL 115347 has no direct cardiac effects and produced insufficient hypotension in our subjects to stimulate a tachycardiac response.

Transdermal application was chosen for use in this study because this route has been shown to yield greater potency and duration of action than intravenous or oral administration in animal models. Side effects in our subjects were those that would be expected from a PGE₂ analogue: they were primarily related to local vasodilatation at the site of drug application (e.g., flushing, induration, erythema). In general, the drug was well tolerated with adequate subject acceptance.

This report includes prospective data from three centers. The protocols were prospectively designed and were the same with respect to duration, days on drug or placebo, diet, and collection of vital signs. Differences included the collection of additional data in Boston with respect to hormones, urinary electrolytes, and assessment of vascular responses to ANG II. The drug dosage differed over a narrow range, but the blood pressure responses were remarkably similar at all centers.

In conclusion, chronic administration of CL 115347, the first PGE₂ analogue available for long-term study in humans, produced a modest reduction in blood pressure. We postulate that this response is limited by compensatory increases in vasopressor hormonal systems and renal sodium retention. Because it produced several of the same compensatory responses seen with other direct vasodilators, CL 115347 does not appear to be useful as an agent for monotherapy of hypertension. However, its effectiveness in combination with other agents, such as β-blockers and diuretics, merits further study, as does its use in other disease states, such as congestive heart failure or peripheral vascular disease.

Acknowledgment

We thank Dr. Norman Hollenberg for his generous assistance in determining PAH and inulin clearances in our patient samples.

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