Systemic Vasoconstrictor and Renal Vasodilator Effects of PLV-2 (Octapressin) in Man

By Jay N. Cohn, M.D., Felix E. Tristani, M.D., and Ibrahim M. Khatri, M.B., B.S.

SUMMARY

The systemic and renal hemodynamic effects of PLV-2 (octapressin) were studied in patients with hypotension or decompensated cirrhosis of the liver. Low doses (0.004 to 0.02 units/min) increased renal blood flow (indicator-dilution technique), reduced renal vascular resistance, and produced a slight increase in arterial pressure and systemic vascular resistance. Higher doses (0.1 to 0.5 units/min) produced a sharp increase in arterial pressure and systemic resistance while renal resistance increased moderately and renal blood flow usually was maintained above control levels. Renal fraction was increased at all dose levels. The increased renal blood flow was accompanied by more rapid intrarenal dye transit time and slight increase in renal extraction ratio of para-aminohippurate suggesting a rise in cortical blood flow. It is concluded that PLV-2 in small doses produces renal vasodilatation and in larger doses preferential extra-renal vasoconstriction resulting in redistribution of blood flow to the kidney.

Additional Indexing Words:
Angiotensin Renal cortical blood flow
Renal dye curves Norepinephrine Cardiac output

Although vasopressin preparations have been available for many years, they have never been widely employed for their vascular effects. The lack of interest in these substances as therapeutic agents may be related to the observations that they have a weak and unpredictable pressor effect in man which occurs only in doses producing marked antidiuresis,1-3 and that they may induce coronary vasoconstriction.4

A synthetic analogue of lysine vasopressin (octapressin; PLV-2) became available several years ago,5 and when compared to the natural vasopressins, it was found to have enhanced vascular effects and greatly reduced antidiuretic properties.6 While PLV-2 was reported to be a dependable and apparently well-tolerated pressor agent,6-8 its clinical use has been limited mostly to the management of bleeding esophageal varices on the basis of its splanchnic vasoconstrictor activity.9

In the present study it has been found that PLV-2 has the unique property of producing renal vasodilatation combined with systemic vasoconstriction, thus leading to a redistribution of blood flow to the kidney. It is suggested that the vascular effects of the drug may have potential therapeutic application when hypotension and renal hypoperfusion coexist.

Methods

Studies were performed on patients with hypotension or decompensated cirrhosis of the liver. One patient (R. W.) had shock associated with pneumonia. The other 10 patients were alcoholics with severe cirrhosis of the liver accompanied by ascites. Four of these patients (J. R., J. H., J. M., and F. J.) had oliguria and azotemia as manifestations of the spontaneous renal failure of cirrhosis. Five of the cirrhotic patients exhibited resting systolic arterial pressures of less than 100 mm Hg.

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The right femoral artery and vein were cannulated by the Seldinger technique and radio-opaque polyethylene catheters were advanced under fluoroscopic guidance into a renal artery and the corresponding renal vein. Position of the catheters was confirmed in many instances by the injection of a small amount of contrast material. Arterial pressure was monitored with a Statham P23Db strain-gauge transducer and a Sanborn recorder. Cardiac output (CO) was determined in duplicate by the indicator-dilution technique. Indocyanine green was injected as a bolus into the right atrium or renal vein while renal arterial blood was withdrawn at a constant rate through a Gilford cuvette densitometer. Renal blood flow (RBF) was determined in individual kidneys by an indicator-dilution technique.\(^{10}\) Indocyanine green, 0.625 mg, was injected into the renal artery while renal venous blood was sampled through the cuvette. The recorded curves were analyzed by the standard Stewart-Hamilton method. Reported values for RBF represent averages of two or three successive curves that varied by less than 10%. The appearance time, peak concentration time, and mean renal transit time of the dye were corrected for catheter and cuvette delay. Renal blood volume in ml/kidney was calculated as the product of RBF (ml/sec/kidney) and mean transit time (MTT) (sec).

Total systemic vascular resistance (SVR) in dyne-sec cm\(^{-5}\) was calculated from the formula:

\[
SVR = \frac{(MAP - RAP) \times 1332 \times 60}{CO \text{ (ml/min)}}
\]

where MAP is the mean arterial pressure and RAP the mean right atrial pressure in mm Hg. RAP was assumed to be zero when only inferior vena caval pressure was measured in patients with ascites.

RBF was taken as twice the blood flow measured in individual kidneys, assuming equal flow to both kidneys. Renal vascular resistance (RR) in dyne-sec cm\(^{-5}\) was calculated from the formula:

\[
RR = \frac{(MAP - RVP) \times 1332 \times 60}{RBF \text{ (ml/min)}}
\]

where RVP is the mean renal venous pressure.

Renal fraction (RF) was calculated from the formula:

\[
RF = \frac{RBF}{CO}
\]

Following control observations PLV-2,\(^*\) 25 units, diluted in 200 ml of 5% of dextrose in water, was administered as a constant intravenous infusion. In some patients the infusion was given by intravenous drip which was adjusted to produce the desired pressor effect. In other patients the drug was administered by a Harvard infusion pump at a rate of from 0.03 to 2.0 ml/min (0.004 to 0.25 units/min). When arterial pressure had stabilized for 15 to 30 min on a constant infusion of the drug, hemodynamic studies were repeated. If more than one dose of PLV-2 was given to a patient, studies were performed first on the lowest dose and then the infusion rate was progressively increased.

Results

Systemic Hemodynamic Effects

Intravenous infusion of PLV-2 resulted in a dose-related increase in arterial pressure and total systemic vascular resistance (table 1, figs. 1 and 2). Blood pressure usually rose within 15 sec after the infusion was begun and the pressor effect waned gradually over a 30-min period after the infusion was stopped. The cardiac output response was variable, falling slightly in seven of the patients and either increasing or remaining unchanged in the other four. Heart rate was only slightly altered by the drug. Small doses were accompanied by an insignificant fall from 91 to 87 beats/min while larger doses induced slight cardiac slowing from an average of 94 to 85 beats/min.

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\*Supplied by Sandoz Pharmaceuticals, Hanover, New Jersey.

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Figure 1

Changes in arterial pressure and renal blood flow during intravenous infusion of PLV-2 in eight subjects. C = control values. Connected dots represent observations during progressively increasing infusion rates of the drug.

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Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>MAP (mm Hg)</th>
<th>RR (mm Hg)</th>
<th>CO (L/min)</th>
<th>SVR (dyne-sec cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.S.</td>
<td>104</td>
<td>120</td>
<td>5.13</td>
<td>1.35</td>
</tr>
<tr>
<td>W.M.</td>
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<td>122</td>
<td>5.38</td>
<td>1.30</td>
</tr>
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<td>H.E.</td>
<td>104</td>
<td>124</td>
<td>5.31</td>
<td>1.32</td>
</tr>
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<td>R.W.</td>
<td>106</td>
<td>128</td>
<td>5.48</td>
<td>1.34</td>
</tr>
<tr>
<td>D.R.</td>
<td>104</td>
<td>130</td>
<td>5.11</td>
<td>1.33</td>
</tr>
<tr>
<td>J.H.</td>
<td>102</td>
<td>124</td>
<td>5.22</td>
<td>1.32</td>
</tr>
<tr>
<td>J.E.</td>
<td>104</td>
<td>124</td>
<td>5.11</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Figure 2

Average values in eight patients given both low and high dose infusions of PLV-2.

Stroke volume was not significantly altered. Venous pressure measured in the renal vein, inferior vena cava, or right atrium showed only negligible and inconsistent changes.

Renal Hemodynamic Effects

Intravenous infusion of PLV-2 in a dose of approximately 0.004 units/min produced a slight increase in arterial pressure and a rise in RBF (fig. 1). In one patient renal vasodilatation occurred with a dose insufficient to alter blood pressure. As the dose was increased, the pressor effect became more marked and RBF fell, although in many patients it remained higher than in the control period.

For purposes of analysis the responses to intravenously administered PLV-2 were divided into low dose effects (0.004 to 0.02 units/min) and high dose effects (0.1 to 0.5 units/min). Low doses of PLV-2 produced an increase in renal blood flow (RBF) and a decrease in renal vascular resistance (RR) (table 1). RBF increased in nine patients from an average of 604 to 830 ml/min ($P < 0.01$), while mean arterial pressure (MAP) increased an average of 10.2 mm Hg and RR fell from an average of 8,537 to 6,967 dyne-sec cm⁻² ($P < 0.05$). The renal fraction of cardiac output (RF) increased from 9.1 to 14.6% ($P < 0.01$) (fig. 3).

With high dose infusions, renal resistance increased and RBF usually was lower than

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with the smaller doses. However, in seven of 10 subjects, RBF remained higher than in the control period (table 1). RBF averaged 870 ml/min during high dose infusions compared to a control of 760 ml/min (P > 0.05). MAP was increased an average of 26.2 mm Hg, and RR rose from a control of 8,090 to 9,867 dyne-sec cm⁻⁵ (P < 0.05). The RF was increased from 10.6 to 12.9% (P > 0.05) (fig. 3).

Eight patients were given both low and high dose infusions (fig. 2). In each instance the highest RBF was attained during low dose administration, but in five of the subjects, the RBF attained during administration of high doses still was higher than that in the control period. RR fell during low dose infusion in six of the eight patients and increased above control values during high dose infusion in all but one subject. RF averaged 8.8% in the control period, 13.1% with low doses, and 10.7% with high doses.

Configuration of the renal dye curves was predictably altered by PLV-2. The dye appearance time was shortened by low doses from an average of 3.7 to 2.5 sec (P < 0.05), and the time from dye injection to peak concentration was shortened from an average of 8.2 to 6.0 sec (P < 0.05). The interval between dye appearance and peak concentration was shortened by PLV-2 in every subject (P < 0.01).

Since RBF was increased and mean transit time was shortened, changes in calculated renal blood volume were not consistent. In six patients volume increased during PLV-2 infusion, and in the other five subjects it either was not altered or fell slightly.

The renal extraction ratio of para-aminohippurate (PAH) was determined in six patients (table 2). The average PAH-extraction ratio was 0.51 in the control period; it either remained the same or increased slightly during infusion of PLV-2. Thus, the increase in total renal blood flow during PLV-2 infusion was distributed to tissue which extracted PAH in at least as great a proportion as the control RBF.

Renal Arterial Infusion
In two subjects the renal vasoactive properties of PLV-2 were tested by infusing the drug directly into the renal artery and measuring blood flow in the perfused kidney. In one hypertensive subject an infusion of 0.00003 units/min produced a small, but definite, increase in kidney blood flow from 535 to 621 ml/min/kidney. This very small infusion rate of the drug was associated with a 6-mm Hg rise in MAP and a fall in R-R from 14,355 to 12,945 dyne-sec cm⁻⁵. In the other subject (R. W.) a much larger renal arterial infusion of 1 unit/min produced a marked systemic pressor effect without much change in RBF.

Table 2

<table>
<thead>
<tr>
<th>PAH-Extraction Ratios in Six Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>A.S.</td>
</tr>
<tr>
<td>W.M.</td>
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<tr>
<td>H.E.</td>
</tr>
<tr>
<td>D.R.</td>
</tr>
<tr>
<td>D.H.</td>
</tr>
<tr>
<td>J.M.</td>
</tr>
<tr>
<td>Average</td>
</tr>
</tbody>
</table>

*High arterial PAH concentration (4-5 mg%).
For abbreviations see table 1.
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MAP increased 26 mm Hg and CO fell by 1,100 ml/min, while kidney blood flow fell only from 320 to 304 ml/min/kidney. Total systemic vascular resistance therefore rose by 77% while the resistance in the perfused kidney increased by only 35%.

Comparison with Norepinephrine and Angiotensin

Equipressor doses of norepinephrine (Levodopa bitartrate) and PLV-2 were administered to one hypotensive patient (fig. 4). Although CO was slightly higher and total systemic vascular resistance lower during the infusion of norepinephrine, RBF was considerably higher during PLV-2 infusion, and renal resistance was less.

In another subject (H. E.) equipressor doses of angiotensin amide (Hypertensin) and PLV-2 were administered. RBF was 750 ml/min during angiotensin infusion and 1,020 ml/min during PLV-2 infusion. Renal resistance was 9,128 dyne-sec cm⁻⁵ during angiotensin infusion and only 6,825 dyne-sec cm⁻⁵ during PLV-2 infusion.

Side Effects

Low doses of PLV-2 usually produced no subjective symptoms, although facial pallor indicating cutaneous vasoconstriction often was detectable even with the smallest doses used. With higher infusion rates, skin pallor was always evident, and the patients often experienced abdominal cramps and the urge to defecate. None of the patients complained of headache, chest pain, or dyspnea, and the electrocardiogram, when monitored during the infusion, was not altered. No evidence of tachyphylaxis was noted during infusions lasting up to 4 hours.

Discussion

Previous studies with natural and synthetic vasopressin have suggested that they may increase renal blood flow. However, the results have been variable. Synthetic vasopressin increased the RBF in anesthetized cats and rabbits but not in conscious dogs or humans. PLV-2, which may have vascular effects qualitatively similar to those of vasopressin, increased RBF in dogs with hemorrhagic or endotoxin shock but not in normotensive dogs or human subjects. Barer has concluded that renal vasodilatation following both lysine vasopressin and PLV-2 is peculiar to the anesthetized animal.

In the present study a renal vasodilator effect of PLV-2 was demonstrated consistently in unanesthetized human subjects. Intravenous infusion of small doses of the polypeptide produced slight increases in arterial pressure and in total systemic vascular resistance and led to a sharp increase in RBF and a fall in renal vascular resistance. That the decrease in renal resistance was not merely the passive effect of an increase in arterial pressure is demonstrated by the observation in one subject of an increase in RBF without a change in arterial pressure. Furthermore, direct renal arterial infusion of a very small dose of PLV-2 in one subject also led to a fall in renal vascular resistance.

The vascular effects of PLV-2 appear to be unique. No other known agent dependably raises the blood pressure by producing systemic vasoconstriction while at the same time dilating the renal vascular bed. Indeed, most vasoconstrictor substances produce intense renal vasoconstriction which usually leads to a reduction in the renal fraction of cardiac output. The renal vasoconstrictive properties of
norepinephrine and angiotensin were compared at equipressor doses to PLV-2 in this study; in each instance the vasopressin polypeptide produced higher RBF and lower renal resistance.

The renal vascular effects of PLV-2 vary strikingly with the dose. While low doses (less than 0.02 units/min) produce almost pure renal vasodilatation, higher doses cause renal vasoconstriction. The renal vasoconstriction is noted only when generalized systemic vasoconstriction has resulted in a considerable increase in arterial pressure. Since the renal vasoconstriction with high doses is considerably less prominent than the extra-renal vasoconstriction, RBF usually is maintained at higher levels than in the control period, and the renal fraction of cardiac output is increased.

If the renal vasoconstriction from larger doses and the renal vasodilatation from smaller doses of PLV-2 both were direct effects of the drug, then dual vascular properties of the polypeptide must be implicated. Since the vasoconstriction only became evident when systemic arterial pressure was considerably elevated and flow usually was supported at or above control RBF, it is possible that the renal response to higher doses of PLV-2 represents at least in part a manifestation of auto-regulation. If the polypeptide had a direct renal vascular effect to account for the increasing renal resistance associated with higher systemic doses, then direct renal arterial infusions of large doses should sharply reduce RBF. However, in one subject given an infusion into the kidney of a dose between two and 10 times the usual systemic dose, RBF in the perfused kidney remained almost constant in the face of a sharp rise in arterial pressure. Texter and his associates also found a very weak renal vasoconstrictor effect of PLV-2 infused into the dog kidney. Under the circumstances of the present study, therefore, PLV-2 may have acted primarily as a renal vasodilator, but when systemic arterial pressure was increased by the drug, intrinsic renal vascular adjustment led to a rise in renal resistance and a return of RBF toward control levels.

The increase in RBF observed in these patients during infusion of PLV-2 was accompanied by a slight rise in the low renal extraction ratio of PAH and by an increase in the rate of dye transit through the kidney. In particular, indocyanine green injected into the renal artery appeared more quickly in the renal vein and reached a peak concentration considerably sooner than it did in the control period. Since the renal transit of blood is most rapid through the cortex, and PAH is extracted most efficiently from cortical blood flow, these observations suggest that PLV-2 increased cortical blood flow in these patients.

The results of the present study cannot necessarily be applied to normal human subjects. All but one of the patients in this series had reduced renal blood flow and more than half were hypotensive. Since none had evidence of significant organic renal disease, it is likely that the low RBF was a manifestation of functional renal vasoconstriction related to shock or cirrhosis. Furthermore, the low PAH-extraction ratio could have signified an alteration in intrarenal distribution of blood flow. The ability of PLV-2 to increase RBF in this setting could be attributed to the inhibition of neurogenic or humoral vasoconstriction, rather than to a direct vasodilator effect of the drug.

The unique hemodynamic effects of this vasopressin analogue in increasing renal perfusion at the expense of extra-renal blood flow may have physiological significance which is as yet unknown. However, use of PLV-2 as a pharmacological agent to increase RBF in patients with renal vasoconstriction, sodium retention, and oliguria has already been tried with encouraging results.

References
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