Polyuria, Polydypsia, and Hypertension Produced by a Six-Day Intravenous Infusion of Prostaglandin E₁ in the Conscious Dog

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SUMMARY The effects of a continuous intravenous infusion of prostaglandin E₁ (PGE₁) on mean arterial pressure (MAP), sodium and water balance, and plasma renin activity (PRA) were examined in 10 conscious dogs maintained on a 70 to 75 mEq/day sodium intake. In a crossover pattern, each dog received 6 days of intravenous PGE₁ (0.1 μg/kg/min) and 6 days of intravenous diluent. When compared to diluent, intravenous PGE₁ resulted in a mild sustained rise in MAP. By Day 6 the intravenous PGE₁, MAP had increased from 98 ± 4 to 112 ± 5 mm Hg (mean ± se) (p < 0.04). Concurrent with the MAP increase, PRA increased from 0.6 ± 0.2 to 3.1 ± 0.7 ng angiotensin I (AI)/ml/hr (p < 0.03). To assess the role of the renin-angiotensin system in the maintenance of the systemic hypertension, AI converting-enzyme inhibitor was given to four dogs on Day 6 of both intravenous PGE₁ and diluent. Only when the dogs were receiving PGE₁ did the administration of converting-enzyme inhibitor result in a significant decrease in MAP (−19 ± 5 mm Hg). In addition to increasing arterial pressure, the chronic infusion of PGE₁ also produced changes in salt and water balance. When compared to diluent, PGE₁ resulted in a twofold increase in both water intake and urine output, an increase in urinary sodium excretion (from 72 ± 3 to 84 ± 6 mEq/day, p < 0.05, on Day 1), and a decrease in urine osmolality (from 942 ± 82 to 586 ± 61 mOsmol/kg H₂O/day, p < 0.05, on Day 1). We conclude that, in the dog, a 6-day intravenous infusion of PGE₁ results in renin-supported hypertension and increased water intake, urine output, and urinary sodium excretion.

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KEY WORDS • prostadlagin E₁ • hypertension • plasma renin activity

The use of acute and chronic infusions of prostaglandins of the E series in the care of neonates with ductus-dependent congenital heart disease has been well documented. In the neonate, fever, apnea, bradycardia, hypotension, seizures, diarrhea, and edema are the well-known side effects of prostaglandin E₁ (PGE₁) infusions. However, little is known of the effect of long-term PGE₁ infusion on salt and water balance, blood pressure, and the renin-angiotensin system. Hockel and Cowley have recently reported that, in the conscious dog, chronic intrarenal PGE₁ infusion promoted a marked diuresis, polydipsia, modest natriuresis, and elevated plasma renin activity (PRA), which eventuated in a state of mild hypertension. They also demonstrated that intravenous PGE₁ produced moderate but directionally similar changes in both renal function and PRA. Since long-term infusions of PGE₁, rather than PGE₂, are used in the infant with congenital heart disease, the present study was designed to assess in the conscious dog the effect of a prolonged intravenous infusion of PGE₁ (6 days) on blood pressure, PRA, and salt and water balance.

Methods

Ten adult mongrel dogs ranging in weight from 23 to 28 kg (25.4 ± 0.9, mean ± se) were kept in metabolic cages at constant temperature and were fed a diet containing 70 to 75 mEq/day of sodium and 55 to 60 mEq/day of potassium. All animals had free access to water and were trained to lie quietly on a padded table, where they were prepared surgically for the experiment.
Surgical Procedures

The animals were anesthetized intravenously (i.v.) with sodium pentobarbital (approximately 25 mg/kg). Through a right thoracotomy, the following polyvinyl catheters were implanted: an arterial, two right atrial, one left atrial, and one thermodilution catheter (Instrumentation Laboratory, Lexington, Massachusetts) in the pulmonary artery. The catheters were exteriorized through a subcutaneous tunnel and protected by a nylon jacket. Catheter patency was maintained by flushing daily with sterile saline and by filling the catheters with heparin (1000 U/ml). All the animals were allowed to recover for 2 weeks before experiments were started.

Arterial and atrial pressures were measured in the trained recumbent dog with P23Db Statham pressure transducers and recorded on a VR-12 optical recorder (Electronics for Medicine, White Plains, New York). Thermal dilution cardiac output was measured with an Instrumentation Laboratory thermodilution recorder model 702. A continuous intravenous infusion of either PGE, or diluent was administered into the right atrium with a Coromed Ambulatory Infusion Pump model ML6 (Coromed Inc., Middleport, New York).

PGE, was dissolved in 95% ethanol 10 mg/ml and stored at 4°C. This served as a stock solution from which an aliquot was then diluted with 0.2 M phosphate buffer and added to the infusion pump twice daily.

Experimental Protocol

After electrolyte and water balance had been established, a 2- to 3-day control period was observed. Then all dogs received a 6-day continuous infusion of 0.1 μg/kg/min of PGE, plus diluent and a 6-day infusion of diluent alone (95% ethanol and 0.2 M phosphate buffer) at 0.8 cc/hr, in a crossover pattern. Ten to 14 days were allowed between infusions. The dose of PGE, (0.1 μg/kg/min) was chosen since this is the dose given to infants. The dogs were observed for 3 to 4 days after termination of the infusion. Between 7 and 10 a.m. during the control, experimental, and recovery periods, blood samples were drawn (for measurements of plasma sodium, potassium, and creatinine concentrations, PRA, hematocrit, and plasma osmolality), and arterial and atrial pressures and cardiac output (CO) were measured. Water intake, urine volume, urinary sodium, creatinine excretion, and urine osmolality were measured daily.

Since the angiotensin I (AI)-converting-enzyme inhibitor blocks the conversion of AI to the physiologically active pressor agent angiotensin II (AII), this drug was used to assess the role of the renin-angiotensin system in the maintenance of the systemic pressure in four dogs. AI-converting-enzyme inhibitor has a number of actions in addition to blocking the conversion of AI to AII, that is, potentiation of the effects of bradykinin and a general peptidase inhibition. Since potentiation of the effects of bradykinin could alter both blood pressure and salt and water balance, we were reluctant to administer converting-enzyme inhibitor to all of our dogs. However, in four dogs, 5 mg of AI-converting-enzyme inhibitor was given as a single intravenous bolus on Day 6, just prior to stopping the intravenous infusion of both PGE, and intravenous diluent alone.

Laboratory Measurements

PRA was measured in duplicate with a radioimmunoassay procedure for AI (New England Nuclear, Boston, Massachusetts). Plasma and urinary electrolyte concentrations were determined with a Instrumentation Laboratory flame photometer.

All values are means ± se. Statistical analyses included Student's t test for paired observations, to determine the significance (p < 0.05) of the difference between intravenous diluent alone and intravenous PGE, infusions, and regression analysis, to express the relationship between mean arterial pressure (MAP) and PRA during intravenous PGE, infusion.

Results

Effects of Prostaglandin E, on Mean Arterial Pressure, Cardiac Output, and Plasma Renin Activity

Figure 1 depicts the changes in MAP, systemic vascular resistance, CO, and PRA that were observed during infusions of PGE, and diluent alone in the six dogs who did not receive AI-converting-enzyme inhibitor. During the first hour of intravenous PGE, infusion, MAP decreased from 98 ± 4 to 92 ± 4 mm Hg. By 24 hours, however, MAP had increased to 101 ± 3 mm Hg and continued to increase to a maximum of 112 ± 5 mm Hg (p < 0.04) by Day 6. CO increased transiently during the first few days of PGE, infusion, but reached statistical significance only during the first hour of the continuous intravenous infusion. Systemic vascular resistance decreased from 37 ± 4 to 29 ± 5 mm Hg/liter/min (p < 0.5) during the first hour of PGE, infusion. By 24 hours, however, systemic vascular resistance had returned to control levels, continued to increase, and reached a maximum value of 44 ± 3 mm Hg/liter/min (p < 0.05) by Day 6. Concurrent with these changes in MAP and vascular resistance, PRA rose progressively from an average value of 0.6 ± 0.2 ng AI/ml/hr to reach 1.0 ± 0.3 at 1 hour, 1.5 ± 0.3 at 24 hours (p < 0.05), and 3.1 ± 0.7 at 5 days (p < 0.03). In addition, a high degree of correlation between the rise in MAP and PRA was observed (r = 0.85, p < 0.001). After the continuous PGE, infusion had been terminated, MAP, CO, systemic vascular resistance, and PRA returned to near control values within 24 hours (Figure 1). The 6-day infusion of intravenous diluent alone caused no significant changes in any of the above parameters (Figure 1).

Figure 2 summarizes the changes in MAP and PRA that occurred in four dogs after 5 μg of AI-converting enzyme had been given as a single intravenous bolus on Day 6, just prior to stopping the intravenous infusion of both PGE, and intravenous diluent alone. When the dogs were receiving a chronic infusion of PGE, the administration of AI-converting-enzyme inhibitor...
resulted in a rapid $19 \pm 5$ mm Hg ($p < 0.01$) decrease in MAP and an increase in PRA to $18.2 \pm 3.2$ ng/ml/hr. Little change in either MAP ($-3 \pm 1$ mm Hg) or PRA ($0.3 \pm 0.1$ ng/ml/hr) was observed when the same dogs were receiving a chronic infusion of diluent alone.

**Effects of Prostaglandin E$_1$ on Urine Output and Water Intake**

Figure 3 summarizes the changes in urine output, water intake, urine osmolality, and serum osmolality that were observed during PGE$_1$ and diluent infusions.
in the six dogs who did not receive AI-converting-enzyme inhibitor. During the first 24 hours of intravenous PGE₁ infusion, there was a twofold increase in both water intake (from 713 ± 58 to 1396 ± 154 ml/day, p < 0.05) and urine output (from 403 ± 46 to 942 ± 168 ml/day, p < 0.05). The polydipsia and polyuria were maintained throughout the 6 days of PGE₁ infusion. Concomitantly, urine osmolality fell from an average control value of 942 ± 82 to 586 ± 61 mOsmol/kg H₂O/day on Day 1 (p < 0.05) and remained significantly less than control throughout the remaining 5 days of infusion. Serum osmolality also tended to decrease during the continuous infusion of PGE₁, but never reached statistical significance. During the first 24 hours after stopping the intravenous infusion of PGE₁, both urine output and water intake approached control values; however, urinary osmolality remained suppressed for 48 hours. Although not depicted in Figure 3, glomerular filtration rate, as measured by endogenous creatinine clearance, did not significantly change throughout the PGE₁ infusion period. Infusion of intravenous diluent alone in the same dogs caused no significant changes in urine output, water intake, or serum and urine osmolality.

**Effects of Prostaglandin E₁ on Plasma and Urinary Sodium and Potassium**

Figure 4 depicts the effects of intravenous PGE₁, and urinary sodium and potassium excretion and plasma sodium and potassium concentrations. During the intravenous infusion of PGE₁, urinary sodium excretion increased from an average control value of 72 ± 3 to 84 ± 6 mEq/day (p < 0.05) on Day 1. During the remainder of the 6 days of continuous PGE₁ infusion, urinary sodium excretion tended to remain increased, but the increase reached statistical significance only on Days 3, 5, and 6. Over the 6 days of continuous intravenous PGE₁, there was a net 52 ± 7 mEq increase in urinary sodium excretion. Following termination of the PGE₁ infusion, urinary sodium excretion decreased from 80 ± 6 to 49 ± 5 mEq/day (p < 0.05). Sodium excretion then returned to control values. During intravenous PGE₁, serum sodium concentration tended to decrease, and the decrease reached statistical significance only on Day 6 (p < 0.05). Urinary potassium concentration was altered only slightly by the infusion of PGE₁, and no significant change was noted in plasma potassium concentration. The infusion of intravenous diluent alone produced no significant changes in serum sodium or potassium concentrations or urinary sodium or potassium excretion.

Hematocrit decreased slightly during PGE₁ infusion, but the change was not statistically significant. Both temperature and weight remained unchanged during the control, experimental, and recovery periods.

Two apparent side effects of chronic PGE₁ infusion were observed. Three of the 10 dogs experienced mild diarrhea on the first day of PGE₁, which was not present on subsequent days. In addition, four of the 10 dogs experienced mild degrees of anorexia, in that it took all day for them to finish eating their food.

**Discussion**

The use of acute and chronic infusions of prostaglandins of the E type has become an integral part of the care of infants with ductus-dependent congenital heart disease. However, little is known in either humans or experimental animals regarding the long-term effects of intravenous PGE₁ on blood pressure regulation, PRA, and salt and water homeostasis.

In agreement with previous reports demonstrating hypotension with acute infusion of PGE₁, we observed a fall in MAP and systemic vascular resistance while the heart rate and CO increased. However, with prolonged infusion of PGE₁, there was a mild, sustained rise in MAP and systemic resistance. By Day 6, MAP had increased by 10 to 13 mm Hg (p < 0.05), and systemic vascular resistance had increased by 4 to 9 mm Hg/liter/min (p < 0.05). Hockel and Cowley have also observed a similar increase in MAP following a 7-day chronic intrarenal infusion of PGE₁.

In contrast with the changes in MAP and systemic vascular resistance, intravenous PGE₁ produced a small increase in PRA within 1 hour. As with arterial pressure, however, PRA increased further as the infusion of PGE₁ continued. By Day 6, PRA had increased
to a value almost five times that observed with the infusion of diluent alone.

Numerous in vivo and in vitro studies have suggested that prostaglandins can influence renin release through at least three mechanisms: 1) via a direct intracellular mechanism at anatomic sites of renal-renin storage; 2) via an indirect renal mechanism possibly through changes in renal hemodynamics, or changes in the macula densa, juxtaglomerular cells, renal tubules, or renal baroreceptors; and 3) via an indirect central-nervous-system-mediated mechanism. It is unlikely that the increased PRA observed with chronic intravenous PGE, was mediated via a direct intracellular mechanism, since Beierwaltes and co-workers have shown in isolated rat glomeruli that PGI₄ alone appears to control the release of renin selectively. Since metabolic clearance studies indicate that as much as one-third of PGE, may escape lung metabolism, it seems likely that, during chronic intravenous PGE, infusions, both renal and cerebral arterial PGE, concentrations are increased. Therefore, the increase in PRA we observed following chronic intravenous infusion of PGE, could be mediated either through the indirect effects of PGE, on the kidney to stimulate renin release and/or through the effects of PGE, on the central nervous system to stimulate renin release.

Regardless of the exact mechanism by which intravenous PGE, enhances renin release, it appeared that the rise in MAP we observed in our dogs was related to the increase in PRA. We base this conclusion on two facts. First, we observed a significant correlation between MAP and PRA. Although the MAP increase appeared to be related to the PRA increase, it was smaller than we would have expected relative to the degree of hyperreninemia. Extrapolation of the data reported by Fray et al. and Caravaggi et al. would predict a pressure rise of 15 to 20 mm Hg for a 2.5 ng/ml/hr increase in PRA. We speculate that the marked diuresis and natriuresis also associated with the intravenous PGE, infusion may have blunted the AI-mediated pressure rise.

Second, we observed a marked decrease in MAP in four dogs following the administration of AI-converting-enzyme inhibitor. However, since converting-enzyme inhibitor also increases plasma bradykinin, it is possible that the fall in blood pressure was due to the increase in bradykinin rather than to blockade of the renin-angiotensin system. This possibility seems unlikely, since converting-enzyme inhibitor significantly decreased arterial pressure only when the four dogs were receiving intravenous PGE, and the PRA was increased (Figure 2).

Even though it appears that the elevation in MAP following a 6-day infusion of PGE, was mediated through the renin-angiotensin system, it is conceivable that either an increase in catecholamine release or an increase in plasma vasopressin could also have contributed to the rise in MAP. However, both of these possibilities seem unlikely. First, prostaglandins of the E series are known to be potent inhibitors of both neurally induced norepinephrine release and effector responses. Second, even though prostaglandins are known to cause plasma vasopressin to increase, the fact that in our experiment the chronic infusion of PGE, also produced a significant fall in urine osmolality makes it unlikely that a significant increase in plasma vasopressin occurred.

As with changes in MAP and PRA, the chronic intravenous infusion of PGE, produced significant changes in salt and water balance that were qualitatively similar to those observed with the intrarenal infusion of PGE₂. During the first 24 hours of intravenous PGE₂, there was a significant increase in both urine output and water intake. We speculate that the significant increase in water intake that occurred was probably the result of AII acting on the thirst center. However, since water intake was not controlled, we do not know if the increased urine output and urinary sodium excretion were the direct result of the polydypsia or due to the intrarenal and/or intracerebral effects of PGE₂. Further experiments in animals with controlled water intake would help to clarify this point.

In summary, the present study demonstrates that significant changes in renal handling of water and electrolytes, in PRA, and in MAP occur during a chronic intravenous infusion of PGE, in the dog. Since PGE₂, in doses similar to those used in our experiment, is currently being used in newborn infants, we feel that blood pressure, PRA, and salt and water balance should be carefully monitored in these infants.

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