Laboratory Investigation

Preservation of renal blood flow during hypotension induced with fenoldopam in dogs

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The introduction of drugs that could induce hypotension with different pharmacological actions would be advantageous because side effects unique to a specific drug could be minimized by selecting appropriate therapy. Specific dopamine-1, (DA_1) and dopamine-2 (DA_2) receptor agonists are now under clinical investigation. Fenoldopam mesylate is a specific DA_1 receptor agonist that lowers blood pressure by vasodilatation. The hypothesis that fenoldopam could be used to induce hypotension and preserve blood flow to the kidney was tested. Systemic aortic blood pressure and renal blood flow were measured continuously with a carotid arterial catheter and an electromagnetic flow probe respectively, in order to compare the cardiovascular and renal vascular effects of fenoldopam and sodium nitroprusside in ten dogs under halothane general anaesthesia. Mean arterial pressure was decreased 30 ± 8 per cent from control with infusion of fenoldopam (3.4 ± 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 34 ± 4 per cent with infusion of sodium nitroprusside (5.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) (NS). Renal blood flow (RBF) increased during fenoldopam-induced hypotension 11 ± 7 per cent and decreased 21 ± 8 per cent during sodium nitroprusside-induced hypotension ($P < 0.01$). Sodium nitroprusside is a non-selective arteriolar and venous vasodilator that can produce redistribution of blood flow away from the kidney during induced hypotension. Fenoldopam is a selective dopamine-1 (DA_1) receptor agonist that causes vasodilatation to the kidney and other organs with DA_1 receptors and preserves blood flow to the kidney during induced hypotension.

L'introduction d'agents qui induisent l'hypotension par des actions pharmacologiques différentes pourrait être avantageuse afin de minimiser les effets secondaires spécifiques des agents par une thérapie sélective appropriée. Des agonistes spécifiques des récepteurs dopamine-1 (DA_1) et dopamine-2 (DA_2) sont actuellement investigués. Le fénoldopam mésylate est un agoniste spécifique des récepteurs DA_1 qui diminue la pression artérielle par vasodilatation. On a testé l'hypothèse que le fénoldopam pourrait être utilisé pour induire l'hypotension et préserver le flot rénal. Afin de comparer les effets cardiovasculaires et rénaux du fénoldopam et du nitroprussiate de soude chez dix chiens anesthésiés à l'halothane, on a mesuré la pression artérielle systémique et le flot rénal avec un cathéter carotidien et un débitmètre électromagnétique. La pression artérielle moyenne diminua de 30 ± 8 pour cent du contrôle avec la perfusion de fénoldopam 3,4 ± 2,0 $\mu g \cdot kg^{-1}$) et 34 ± 4 pour cent avec l'infusion de nitroprussiate de soude (5,9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) (NS). Le flot sanguin rénal (RBF) augmenta durant l'hypotension induite par le fénoldopam 11 ± 7 pour cent et diminua de 21 ± 8 pour cent durant l'hypotension induite par le nitroprussiate de soude ($P < 0,01$). Le nitroprussiate de soude est un vasodilatateur non-sélectif artériolaire et veineux qui peut produire une redistribution de flot sanguin loin des reins durant

Key words

ANAESTHETIC TECHNIQUES: hypotensive, fenoldopam, sodium nitroprusside;
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KIDNEY: blood flow;
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l'hypotension induite. Le fénoldopam est un agoniste des récepteurs DA_1 qui provoque une vasodilatation rénale et autres organes ayant des récepteurs DA_1 préservant ainsi le flot sanguin rénal durant l'hypotension induite.

Deliberate induced hypotension during anaesthesia is a common technique to facilitate surgery and reduce blood loss. Despite the increased utilization of induced hypotension during surgery, there has been relatively little research to find new hypotensive agents for this purpose. Sodium nitroprusside (SNP) continues to be the most commonly used agent because of its potency, rapid onset and short duration of action. However, its administration may decrease blood flow to vital organs, and prolonged intravenous infusion may be associated with high levels of toxic metabolites and rebound hypertension that complicate management.[1,2] Such side effects and limitations with hypotensive agents could preclude the use of induced hypotension for some patients who would otherwise benefit from this technique. Clearly, the introduction of an agent that could induce hypotension without these limitations would be advantageous. The availability of a larger group of drugs with different pharmacological actions should make it possible to design more appropriate therapy.

Among the new classes of agents that are now under clinical investigation[3,4] are specific dopamine-1 and dopamine-2 receptor agonists. Both decrease blood pressure: dopamine-1 agonists, by vasodilatation; dopamine-2 agonists, by inhibiting the release of norepinephrine from sympathetic nerve endings. Fenoldopam mesylate, a benzazepine derivative, is the first selective dopamine-1 receptor agonist that has been studied clinically.[5] Oral and intravenous administration of fenoldopam to patients with hypertension or congestive heart failure has been shown to decrease blood pressure and increase renal blood flow and sodium excretion.[6–10] Furthermore, when administered intravenously to mildly hypertensive patients, fenoldopam has been shown to be a potent short-acting hypotensive agent.[8,–11] During isoflurane general anaesthesia in the dog, induced hypotension was reliably obtained with fenoldopam and, unlike induced hypotension with sodium nitroprusside, renal blood flow was preserved.[12] We tested the hypothesis that fenoldopam could be used to induce hypotension and preserve renal blood flow during halothane general anaesthesia in the dog. Because halothane has been shown to block sympathetic ganglionic transmission, it was hypothesized that fenoldopam-induced hypotension could be maintained more easily with halothane general anaesthesia than with isoflurane. Because fenoldopam selectively vasodilates the renal vascular bed and other end organs subserved with dopaminergic receptors, it was hypothesized that fenoldopam-induced hypotensive conditions would preserve renal blood flow when compared with hypotension induced by SNP under otherwise identical clinical conditions.

Methods

Institutional approval was obtained to study ten adult unpremedicated male dogs (10–20 kg). Studies conformed to guidelines established by the American Physiological Society and the NIH regarding animal experimentation. Anaesthesia was induced using intravenous surital (15–25 $mg^{-1} \cdot kg$ IV). Following intubation of the trachea, anaesthesia was maintained with 1.0 per cent end-tidal concentration of halothane, 60 per cent N_2O and 40 per cent O_2. The lungs were ventilated by means of an Air-Shields anaesthesia ventilator. End-tidal concentrations of CO_2 were kept between 30–35 mmHg (Engstrom-Emma end-tidal CO_2 analyzer), and halothane concentration was measured with a Puritan-Bennett end-tidal agent analyzer. A catheter was inserted into the left carotid artery for systemic arterial blood pressure measurements. Systolic and diastolic blood pressures were recorded continuously with a Bell and Howell type 4-327-1 transducer at slow speed (0.1 $mm \cdot sec^{-1}$). A Swan Ganz-catheter positioned in the pulmonary artery via the external jugular vein allowed measurement of pulmonary capillary wedge pressure (PCWP), which was maintained between 8 and 11 mmHg by infusion of normal saline through a large-bore peripheral intravenous catheter. The ECG and pulmonary artery blood temperature were monitored, the latter being maintained at 36–37°C by means of humidified gases and a heating blanket. Through a flank incision, an electromagnetically pulsed doppler flow probe (Narco Type RT-510) was secured around the left renal artery with care to avoid vessel constriction. Thirty minutes after surgical preparation, control measurements were obtained of the following: renal blood flow (RBF), heart rate (HR), systolic and diastolic arterial blood pressure (SBF and DBP), cardiac output (CO), and pulmonary capillary wedge pressure (PCWP). All haemodynamic variables were recorded on a Beckman continuous strip recorder.

Experimental design

All dogs had baseline haemodynamic variables measured 30 min after surgical preparation to ensure a stable baseline environment. The dogs then received an infusion of either fenoldopam or SNP in a random manner to decrease mean arterial pressure (MAP) 30 per cent to 60 mmHg. After 15 min of hypotension, haemodynamic variables were measured as above, the infusion was then discontinued and baseline values for haemodynamic

TABLE I Absolute values for each sequence of infusions ± SEM

	Sequence 1				*Sequence 2*			
	Baseline	*Fenoldopam*	*Baseline*	*SNP*	*Baseline*	*Fenoldopam*	*Baseline*	*SNP*
HR (bpm)	118 ± 2	114 ± 3	119 ± 3	115 ± 3	114 ± 1	110 ± 2	117 ± 2	113 ± 3
sBP (mmHg)	112 ± 4	88 ± 3	114 ± 5	89 ± 3	117 ± 5	94 ± 6	111 ± 3	87 ± 3
dBP (mmHg)	84 ± 5	51 ± 4	84 ± 4	46 ± 3	86 ± 5	60 ± 6	76 ± 2	45 ± 3
MAP (mmHg)	94 ± 5	63 ± 4	94 ± 4	62 ± 2	97 ± 5	72 ± 6	90 ± 3	60 ± 2
CO ($L \cdot min^{-1}$)	3.8 ± 0.5	4.1 ± 0.6	3.6 ± 0.3	38 ± 3	4.2 ± 0.7	4.0 ± 0.4	3.5 ± 0.1	3.6 ± 0.1
PCWP (mmHg)	13 ± 1	12 ± 1	12 ± 1	11 ± 1	13 ± 1	12 ± 1	13 ± 1	11 ± 1
RBF ($ml \cdot min^{-1}$)	165–18	153 ± 23	188 ± 23	154 ± 29	167 ± 20	212 ± 24*	171 ± 22	138 ± 17
RVR ($mmHg \cdot ml^{-1} \cdot min^{-1}$)	0.64 ± 0.07	0.58 ± 0.13	0.57 ± 0.07	0.73 ± 0.25	0.68 ± 10	0.41 ± 18*	0.64 ± 0.11	54 ± 10

*$P < 0.05$.
Significance when compared with its own baseline.

variables were allowed 30 min to be reestablished. Next, the second drug (either fenoldopam or SNP) was infused in an identical manner. After a 30-min period to establish steady-state conditions again, the above sequence was repeated in the same order of the initial sequence of drug administration, i.e., each dog received a total of four infusions, the initial order of which was randomly determined. Each infusion was separated by a 30-min interval to reestablish steady-state conditions. MAP was calculated as 1/3 (SBP-DBP) + DBP and renal vascular resistance (RVR) as MAP/RBF. For each variable, the absolute values and the percentage change during both sequences of infusions were calculated. The averages of each sequence of SNP and fenoldopam were also calculated. Values for SNP and fenoldopam were compared using a paired t test with Bonferroni correction when appropriate and $P < 0.05$ as statistically significant. Values are expressed as mean ± SEM.

Results

The results are shown in Tables I, II and III. We obtained moderate hypotension with either fenoldopam or nitroprusside infusions in all ten dogs. Baseline MAP was 94 ± 5 mmHg before the first and 97 ± 5 mmHg before the second infusion of fenoldopam, and 94 ± 4 mmHg before the first and 90 ± 3 mmHg before the second infusion of SNP. The mean doses of fenoldopam and nitroprusside required to decrease MAP 30 per cent were 3.4 ± 2.0 and 5.9 ± 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. Both agents acted rapidly, obtaining the desired reduction in blood pressure within three minutes.

The values for heart rate obtained during hypotension did not differ for SNP and fenoldopam. Average MAP was 67 ± 4 mmHg for fenoldopam and 61 ± 2 mmHg for SNP, representing a decrease of 30 ± 3 per cent for fenoldopam and of 34 ± 1 per cent for SNP (NS). Neither drug produced values that differed significantly from either baseline levels or values produced by the other hypotensive drug for cardiac output or PCWP.

Averaged over both sequences of each drug infusion, there was a trend to increased renal blood flow during infusion of fenoldopam (163 ± 15 to 178 ± 17 $ml^{-1} \cdot min^{-1}$) which did not reach statistical significance while renal blood flow decreased (179 ± 20 to 144 ± 22 $ml^{-1} \cdot min^{-1}$) during SNP infusion, ($P < 0.02$). Within sequences, the effect of fenoldopam on renal blood flow showed a divergent trend with renal blood flow following the first infusion (165 ± 18 to 153 ± 23 $ml^{-1} \cdot min^{-1}$) representing a statistically insignificant change, whereas renal blood flow increased after the second infusion (167

TABLE II Average absolute values for infusions and baselines ± SEM

	Baseline	*Fenoldopam*	*Baseline*	*SNP*
HR (bpm)	115 ± 2	111 ± 2	118 ± 2	113 ± 3
sBP (mmHg)	115 ± 4	90 ± 4	114 ± 4	89 ± 3
dBP (mmHg)	85 ± 4	55 ± 4	81 ± 3	46 ± 2
MAP (mmHg)	96 ± 4	67 ± 4	93 ± 4	61 ± 2
CO ($L \cdot min^{-1}$)	3.9 ± 0.1	3.9 ± 0.1	3.6 ± 0.1	3.7 ± 0.1
PCWP (mmHg)	12 ± 1	12 ± 1	12 ± 1	11 ± 1
RBF ($ml \cdot min^{-1}$)	163 ± 15	178 ± 17	179 ± 20	144 ± 22*
RVR ($mmHg \cdot ml^{-1} \cdot min^{-1}$)	0.67 ± 0.08	0.49 ± 0.09*	0.60 ± 0.08	0.64 ± 0.17

*$P < 0.02$.
Significance when compared with its own baseline.

TABLE III Per cent change from baseline for infusions ± SEM

	Fenoldopam	*SNP*
HR (bpm)	−4 ± 2	−4 ± 2
Systolic BP (mmHg)	−21 ± 2	−22 ± 2
Diastolic BP (mmHg)	−36 ± 3	−44 ± 2
MAP (mmHg)	−30 ± 3	−34 ± 1
Cardiac Output ($L \cdot min^{-1}$)	5 ± 7	4 ± 5
PCWP (mmHg)	−5 ± 2	−6 ± 4
RBF ($ml \cdot min^{-1}$)	11 ± 7	−21 ± 9*
RVR ($mmHg \cdot ml^{-1} \cdot min^{-1}$)	−29 ± 7	−1 ± 15

*$P < 0.01$.
Significance when compared with its own baseline.

± 20 to 212 ± 24 $ml^{-1} \cdot min^{-1}$, $P < 0.05$) (Table I). Renal blood flow was preserved with fenoldopam and decreased with SNP such that the difference between the two treatment groups was significant ($P < 0.01$). The decrease in renal blood flow with SNP was accomplished without a change in renal vascular resistance relative to baseline (0.60 ± 0.08 to 0.64 ± 0.17 $mmHg \cdot ml^{-1} \cdot min^{-1}$), whereas renal vascular resistance was decreased significantly by fenoldopam (0.67 ± 0.08 to 0.49 ± 0.09 $mmHg \cdot ml^{-1} \cdot min^{-1}$, $P < 0.05$).

Discussion

The present study demonstrated a difference in renal blood flow in dogs anaesthetized with halothane during sodium nitroprusside- vs fenoldopam-induced hypotension. Previous studies on the regional haemodynamic effects of SNP revealed that its mechanism of action, vasodilatation of the pre-capillary sphincters, may cause redistribution of blood flow away from certain vascular beds such as the kidney.[1,13]

Both dopamine and fenoldopam have been shown to increase renal blood flow.[3,14] Fenoldopam differs from dopamine in that it lacks alpha and beta adrenoceptors and DA_2 receptor agonist activity at therapeutic concentrations;[5] thus higher doses of fenoldopam do not directly increase either heart rate or blood pressure. Because of its selective action on dopamine-1 receptors, fenoldopam is a potent renal, mesenteric, cerebral, and coronary vasodilator.[5] Fenoldopam also increases urinary flow rate, free water clearance, and fractional excretion of sodium.[8] Previous studies in dogs anaesthetized with isoflurane during sodium nitroprusside- vs fenoldopam-induced hypotension have shown that renal blood flow was preserved with fenoldopam.[12] In this study with halothane, results showed that moderate hypotension can be achieved under general anaesthesia in the dog with fenoldopam as with SNP. Moreover, renal blood flow was preserved when hypotension was induced with fenoldopam, but not when it was induced with SNP. This result is consistent with the fact that fenoldopam exerts selective action at vascular beds subserved by dopamine-1 receptors whereas SNP acts as a nonspecific arteriolar and venous vasodilator.

Because fenoldopam has a rapid onset and short duration of action, it is a useful agent to induce hypotension during general anaesthesia. Pharmacokinetic data of intravenous administration of fenoldopam in hypertensive patients and experimental animals have shown that the drug has an elimination half-life of less than ten minutes.[15]

Although evidence from awake humans suggests that the action of fenoldopam (decreased blood pressure and increased RBF) is relatively attenuated in normotensive compared with hypertensive patients,[16] we believe that fenoldopam can be used with general anaesthesia to induce hypotension in normotensive patients. Hughes *et al.*[17] recently used fenoldopam to demonstrate DA_1 receptors in human skeletal muscle vasculature, suggesting that fenoldopam may dilate vascular beds in the human which are not present in the dog and this may contribute to the hypotensive effect in humans. We used halothane general anaesthesia to reduce any sympathetic ganglionic effect that might have contributed to reflex activity attenuating the hypotensive response seen with fenoldopam in awake patients.[18–20] In addition, we used a greater dose of fenoldopam in our study (5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to induce hypotension than the typical infusion dose used in studies to control hypotension in awake patients (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

The effect of halothane on the normotensive and hypotensive state has been investigated.[21] In the hypovolaemic hypotensive dog, halothane reduced or abolished the effect of renal sympathetic vasoconstriction and thereby allowed renal blood flow to increase toward normal values. This may partially explain the tendency in our experiment for baseline RBF to change over time and increase with fenoldopam during the second infusion in our method of evaluation. Another possible explanation may be that of an unrecognized drug interaction. We waited 30 min after the discontinuation of fenoldopam because its plasma half-life suggested elimination and termination of its effect. The possibility of prolonged effect at the renal artery has not been evaluated and could have potentially influenced subsequent trends. We believe that this effect would have been minimized because the drugs were administered in a randomized manner.

It appears halothane did not offer any advantages for inducing hypotension with fenoldopam, as some dogs remained resistant to both fenoldopam- and SNP-induced hypotension under halothane general anaesthesia. The influence of the renin-angiotensin system, as well as the distribution of DA receptors may be contributing factors that need further investigation before fenoldopam can be recommended as clinically useful.

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