FULL PAPER *Internal Medicine*

Effects of Dopamine Infusion on Cardiac and Renal Blood Flows in Dogs

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(Received 4 June 2001/Accepted 13 September 2001)

ABSTRACT. In veterinary medicine, dopamine is currently being administered clinically by infusion for treatment of kidney disorders at low doses (≤3 μg/kg/min) and for assessment of hemodynamics at high doses (≥5 μg/kg/min). However, since high doses of dopamine cause peripheral vasoconstriction due to its effect on alpha adrenoceptors, high doses have no longer been recommended. The present study was conducted to explore possible regimens for the use of dopamine infusion in dogs. The regional (renal and cardiac) blood flow for 60 min was measured by using colored microspheres at three doses (3, 10 and 20 μg/kg/min) of dopamine infusion in healthy anesthetized mongrel dogs. The effects on kidney and peripheral hemodynamics at each dose and the resultant cardiac output, mean arterial blood pressure and total peripheral resistance were determined. Renal blood flow increased markedly at 3 μg/kg/min dopamine. Improvement in hemodynamics indicated by marked increase in cardiac blood flow, cardiac output and mean arterial blood pressure and decreased total peripheral resistance was observed at higher doses (10 and 20 μg/kg/min). At 10 μg/kg/min, in addition to the satisfactory increase in cardiac blood flow, there was also a stable satisfactory increase in renal blood flow. However, at 20 μg/kg/min, increased myocardial oxygen consumption (manifested by marked increased in cardiac output), arrythmia and irregular increase in renal blood flow were detected. This study suggests that the clinical use of dopamine infusion in dogs could be safely expanded to moderately higher doses.

KEY WORDS: canine, colored microsphere, dopamine, heart, renal.

J. Vet. Med. Sci. 64(1): 41–44, 2002

Intravenous infused dopamine acts on alpha and beta adrenoceptors and specific dopamine receptors, affecting mainly the kidney and cardiovascular system. The pharmacological effects of dopamine are unique sequence of receptor activation and dose dependent. At low infusion rates (≤3 μg/kg/min), dopamine produces vasodilation of renal and coronary arteries due to the action on specific dopamine receptors. And at high infusion rates (≥5 μg/kg/min), activation of beta 1 adrenoceptors leads to increased cardiac output, while activation of alpha adrenoceptors results in vasoconstriction [3, 6, 7, 11, 12]. In veterinary medicine, dopamine is clinically used in treatment of disorders of the kidney and the cardiovascular system depending on its use human medicine [4, 6, 7, 12, 13]. Low doses of dopamine have been administered for treatment of oliguria to improve urine production, which high doses have been given to improve hemodynamics in circulatory shock [5, 9]. However, only few studies have been conducted on the clinical use of dopamine in veterinary medicine. For more effective and safer use of dopamine in that field, more detailed information, including effects of different doses of dopamine on hemodynamics, are needed.

This experiment was conducted primarily to explore possible regimens for the use of dopamine infusion in dogs through measurement of cardiac and renal blood flow, using colored microspheres, and changes in hemodynamics at different doses of dopamine.

MATERIALS AND METHODS

Animals: Surgical and experimental procedures were carried out according to the "Guidelines for Experiments on Animals" at the Tokyo University of Agriculture and Technology. Thirty-nine healthy adult mongrel dogs of both sexes, 7.46–14.38 kg in weight, were used in the study. The dogs were divided into 3 groups according to the dopamine infusion dose. Group A (3 μg/kg/min) consisted of 19 dogs while groups B (10 μg/kg/min) and C (20 μg/kg/min) had 10 dogs each. Group A was considered as the low dose group, which groups B and C as the high dose groups.

Surgery: After administration of atropine sulfate (0.05 mg/kg SC), acepromazine maleate (0.5 mg/kg SC) and thiamylal sodium (10 mg/kg IV), endotracheal intubation was performed on the dogs. Anesthesia was maintained with 0.5–2.0 % isoflurane in 100% oxygen (2 l) and intermittent dosing of suxamethonium chloride (2 mg/head IV), and artificial ventilation was adjusted to keep $PaCO_2$ at 40 mmHg. Following injection of heparin sodium (100 IU/kg) as an anticoagulant, a Formocath 7640 catheter (Bechton-Dickinson and Company, New Jersey) was inserted into femoral artery. An 8 Fr polystyrene catheter was then inserted into the carotid artery and advanced to the aortic arch. Thoracotomy was performed to insert an electromagnetic flow meter probe (Blood Flow Transducer, FB-120, Nihon Koden Inc., Tokyo) at the base of the aortic arch and an 8 Fr polystyrene catheter for injection of microspheres on the left atrium. Throughout the surgical procedure and experiment, lactated Ringers' solution was infused (10 ml/kg/hr IV) to maintain hemodynamics and electrocardiogram (ECG) was recorded from standard limb leads for monitoring of heart function.

Drug: Each dilution (3, 10 and 20 μg/kg/min) of dopamine was prepared in lactated Ringers' solution immediately

before use. Intravenous dopamine infusion was started for 60 min after achieving a steady state, which was reached within about 15 min after completion of the surgical procedure.

Measurement of regional blood flow with colored microspheres: Colored microspheres were used for measurement of renal and cardiac blood flow. This technique has environmental and economic advantages compared to currently used radiolabelled microspheres [1, 15, 19]. Five types (corresponding to the color of the dye used for surface coating: blue, violet, white, red and yellow) of Dye-Track colored microspheres (Triton Technology Inc., California) suspension were used. Each microsphere was injected within 10 sec into the left atrium, successively at 10 min before dopamine infusion (pre), 10 min (D10), 30 min (D30), 60 min (D60) after start of infusion and 30 min after termination (post) of infusion. The injection line was then flushed with 10 m*l* saline. A blood sample, for reference, was withdrawn from the carotid artery, started at 5 sec before the microspheres injection and continued for 1 min at a rate of 6.0 m*l*/min. The reference blood sample was mixed with digestive solution [16 N KOH and 20% polyoxyethylenesorbitanmonooleate (Tween 80, Wako, Osaka) in deionized water]. After completion of the injection of microspheres, the dog was euthanized under deep anesthesia by exsanguination and the kidney and heart were removed. The weight of the organs were measured, tissue samples were collected and cut into small pieces and digested for over 48 hr with sufficient digestive solution (4 N KOH with 2% Tween 80 in deionized water). In order to retain the microspheres, each pre-warmed digestive sample was filtered under vacuum suction through a 10-μm pore PE-membrane filter. The filtration membrane was rinsed with 2% Tween 80 and 70% ethanol, and gently placed into a micro tube. The dye was recovered from the microspheres by adding 100 μl of N, N-dimethylformamide and centrifuging at 2,000 g for 5 min. The photometric absorption of each dye solution was measured by spectrophotometer (wave length range 190–820 nm with 2-nm optical band width). Using the MISS software, calculations of regional blood flow, expressed as flow per gm per min, were performed using the following formula: $Flow_{tissue}=(Microsphere_{tissue} \times Flow_{reference})/Microsphere_{reference}$.

Determination of cardiac output (CO), mean arterial blood pressure (MAP) and total peripheral resistance (TPR): In addition to measurement of the regional blood flow, CO (l/min), MAP (mmHg) and TPR were determined. CO was measured by an electromagnetic flow meter (MFV-3200, Nihon Koden). Diastolic, systolic and mean arterial blood pressures were measured through a femoral artery catheter connected to a pressure transducer (Lifekit, DX-360, Nihon Koden). CO and MAP were continously recorded on a polygraph system (RM-6000, Nihon Koden). TPR was calculated using the formula: TPR=MAP/CO.

Data analysis: All values were tested by Thompson test ($p<0.05$). Because of wide variations in measured values between dogs, all values shown are means expressed as percent change. For comparison, the pre value was designated as 100%. All values are expressed as means ± SE. Paired data obtained before and after dopamine infusion values were compared with a nonparametric Wilcoxon rank sum test using data analysis software (Statview Ver. 4.5, Abacus Concepts, Berkley) at $p<0.05$. Comparison of the results between different doses was also carried out.

RESULTS

All animals exhibited no apparent clinical abnormalities during the course of the surgery and experiments except two dogs in Group C (20 μg/kg/min dopamine infusion), where ventricular arrhythmia was detected intermittently by ECG. However, the dogs' conditions returned to normal, so the experiment was proceeded according to the proposed plan.

Renal blood flow (RBF): RBF rates before, during and after dopamine infusion for each group are shown in Fig. 1. In Group A, RBF increased rapidly and markedly at D10 (167.63 ± 23.08%) and was maintained at the same level afterwards. In Group B, RBF increased gradually; its peak at D60 (164.13 ± 12.59%) was similar to that of Group A at D60 (168.00 ± 15.15%). In Group C, RBF increased at D10 (146.44 ± 4.98) and D60 (156.63 ± 12.18%) but declined at D30 (106.55 ± 15.13%). During dopamine infusion, RBF tended to increase in all groups, but the greatest increase was observed in Group A. After termination of dopamine infusion, RBF values in all groups were restored to those of pre-dopamine infusion level.

Cardiac blood flow (CBF): The rates of CBF before, during and after dopamine infusion are shown in Fig. 2. In Group A, CBF increased rapidly at D10 (140.11 ± 18.04%), followed by non-significant increase. In Group B, CBF did not significantly changed at D10, but markedly increased at D30 (229.72 ± 52.99%) and thereafter slightly declined at D60 (176.60 ± 14.04%). In Group C, CBF increased rapidly at D10 (173.40 ± 17.49%), and thereafter increased gradually and peaked at D60 (221.30 ± 31.93%). During dopamine infusion CBF had a tendency to increase in all groups, with marked increases at high doses (Groups B and C). The peaks of CBF in Groups B (D30) and C (D60) were similar. After termination of dopamine infusion, CBF values in all

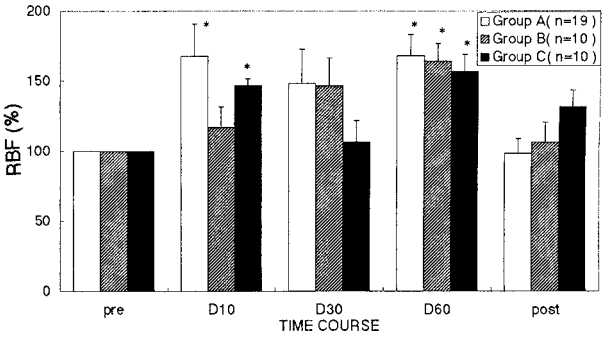

Fig. 1. Percentage rate of RBF before (pre), during (D10, D30, D60) and after (post) dopamine infusion in dogs (* $p<0.05$).

groups returned to those of pre-dopamine infusion level.

Cardiac output (CO): The values of CO before, during and after dopamine infusion are shown in Fig. 3. In Group A, no significant differences among the values were found during infusion of dopamine. In high dose groups, CO values increased significantly during dopamine infusion; the highest value was recorded at D30 (151.92 ± 8.94%) in group C, and decreased after termination of dopamine infusion, with a significant decrease detected in Group B (84.17 ± 6.14%).

Mean arterial blood pressure (MAP): The values of MAP before, during and after dopamine infusion are shown in Fig. 4. In Group A, no significant differences among the values were found during dopamine infusion. The values of MAP during dopamine infusion increased markedly or significantly in high dose groups. The highest value was recorded at D60 (135.93 ± 6.05%) in Group C. After termination of dopamine infusion, MAP values in all groups returned to those of pre-dopamine infusion levels.

Total peripheral resistance (TPR): TPR values before, during and after dopamine infusion are shown in Fig. 5. In Group A, no significant differences among the values were found during dopamine infusion. TPR decreased significantly in Group B at D10 (90.08 ± 3.04%) and D30 (88.27 ± 4.29%) and in Group C at D10 (84.72 ± 5.8%). After termination of dopamine infusion, TPR values in all groups returned to those of pre-dopamine infusion levels.

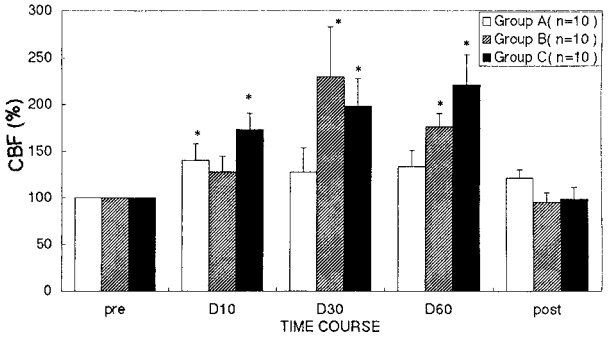

Fig. 2. Percentage rate of CBF before (pre), during (D10, D30, D60) and after (post) dopamine infusion in dogs (* $p<0.05$).

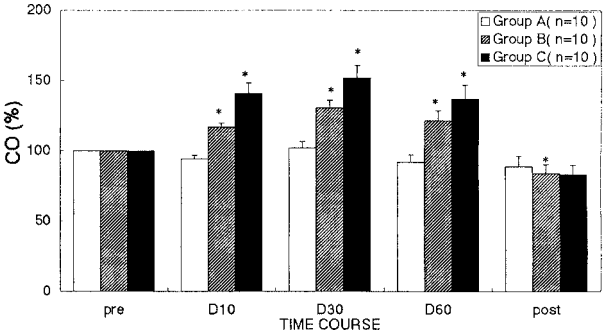

Fig. 3. Percentage rate of CO before (pre), during (D10, D30, D60) and after (post) dopamine infusion in dogs (* $p<0.05$).

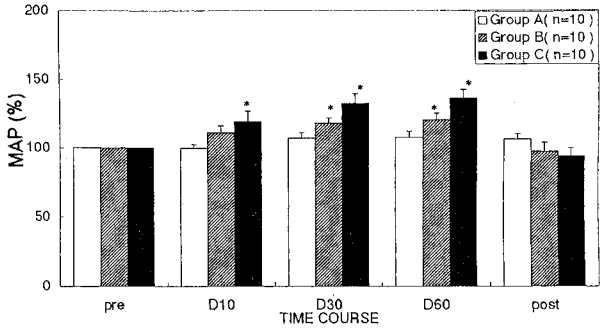

Fig. 4. Percentage rate of MAP before (pre), during (D10, D30, D60) and after (post) dopamine infusion in dogs (* $p<0.05$).

DISCUSSION

At low infusion dose of dopamine, the increases of renal and cardiac blood flows without accompanying increase in cardiac output observed in the study may be underlied by the effect of dopamine on specific dopamine receptors. This effect has been observed particularly on the kidney [6, 11, 12]. However, since there were only a slight increase at D10 in cardiac blood flow and no effects on other parameters (CO, MAP and TPR) at low dose, it is suggested that dopamine at low dose has no significant effect on systemic hemodynamics.

The CO values after termination of dopamine infusion at high doses were decreased, but this reduction apparently has no effect on other post-infusion values. And improvement in systemic circulation was observed at higher infusion doses of dopamine in this study. The augmentation of cardiac contractility can be due to activation of beta 1 adrenoceptor by dopamine with secondary increase in renal blood flow [4, 6, 12, 17]. The effect of dopamine infusion on systemic hemodynamics is dose-dependent which higher doses cause more significant effects.

The decrease in TPR at high doses can be attributed to the higher in cardiac output compared to the mean arterial blood pressure. The marked increases in both cardiac output indicates increase in cardiac strength and myocardial oxygen consumption; therefore it is necessary to consider the cardiac muscle load at high dose infusion [10]. Because of this and the possible occurrence of arrythmia, dopamine infusion at high doses must be carefully monitored [5, 9]. It has been observed that vasoconstriction due to the action of dopamine on alpha adrenoceptor at high doses has a harmful effect on regional blood flow [14, 16]. This could explain the unstable increase in renal blood flow observed in dogs given high infusion dose (20 μg/kg/min) of dopamine.

In the present study, infusion of dopamine at a rate of 10 μg/kg/min affected cardiac blood flow and caused changes in cardiac blood flow similar to that obtained at 20 μg/kg/min dose. This suggests that there were no differences con-

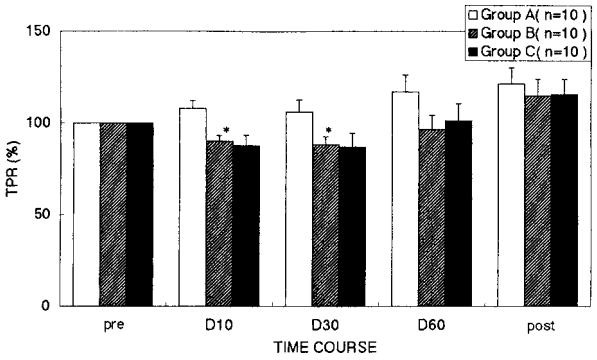

Fig. 5. Percentage rate of TPR before (pre), during (D10, D30, D60) and after (post) dopamine infusion in dogs (* $p<0.05$).

cerning protection of cardiac muscle between both groups [8].

In conclusions, the higher doses (> 5 μg/kg/min) of dopamine can be used for treatment of complications resulting from renal and heart failure, because the results of this study show that the dosage of dopamine can be increased to 10 μg/kg/min without causing abnormal clinical signs. And the study for pathological model may be needed to practical use of dopamine more safely.

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