Transpl Int (1994) 7: 388–391

ORIGINAL ARTICLE

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Vasoconstrictor effect of cyclosporin on the mesenteric artery in the dog

Received: 1 November 1993
Received after revision: 28 February 1994
Accepted: 16 March 1994

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Abstract To evaluate the effect of cyclosporin (CyA) on the mesenteric arterial bed, studies were performed on the isolated mesenteric artery perfused at a constant flow in 20 dogs. Changes in mesenteric perfusion pressure reflected variations in vascular resistance. Pure powder CyA was dissolved in autologous blood and injected at doses of 5, 10, 20 and 40 mg. Infusions of 5 and 10 mg CyA caused nonsignificant mean increases of 3 ± 2 mm Hg [95 % confidence interval (CI) – 2 to + 7; $P > 0.05$] and 3 ± 3 mm Hg (95 % CI – 3 to + 9; $P > 0.05$) in mesenteric perfusion pressure, with CyA blood levels in the mesenteric vein averaging 466 ± 153 and 692 ± 130 nmol/l, respectively, at the end of the injections. Infusions of 20 and 40 mg CyA caused significant increases in mesenteric perfusion pressure averaging 11 ± 3 mm Hg (95 % CI 3–18; $P < 0.05$) and 26 ± 4 mm Hg (95 % CI 16–34; $P < 0.05$), respectively. CyA blood levels at the end of infusion averaged 806 ± 85 and 1118 ± 89 nmol/l, respectively, in the mesenteric vein. Blockade of alpha-adrenergic receptors with phentolamine abolished the CyA vasoconstriction of the mesenteric artery, with the increase in perfusion pressure averaging 16 ± 4 mm Hg before and 3 ± 3 mm Hg after phentolamine ($P < 0.05$). Thus, in the dog, CyA causes an acute vasoconstriction of the mesenteric artery through stimulation of alpha-adrenergic receptors.

Key words Cyclosporin, vasoconstriction, dog · Vasoconstriction, cyclosporin, dog · Mesenteric artery, cyclosporin, dog

Introduction

Cyclosporin (CyA) has become the immunosuppressive drug of choice in organ transplantation. CyA has been shown to cause renal and peripheral arterial vasoconstriction that could be largely responsible for the high incidence of hypertension and renal insufficiency among patients undergoing solid organ transplantation [8, 10]. Experimental and clinical studies have suggested that renal arterial vasoconstriction is due to a local increase in endothelin and thromboxane release, whereas that of the femoral artery is caused by a systemic increase in adrenergic activity [1, 11, 15].

The direct effect of CyA on the mesenteric artery remains unknown, and it has not yet been determined if CyA affects vessels other than the renal and femoral arteries. The objective of the present study is to define the effect and the mechanism of action of CyA on the mesenteric artery in the dog. The hypothesis is that CyA causes a dose-dependent vasoconstriction of the mesentric artery and that this effect is mediated by the adrenergic system.

Materials and methods

Twenty mongrel dogs weighing 20–30 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and artificially ventilated, after endotracheal intubation, at 10–12 cycles per minute using a Harvard ventilator (Harvard Apparatus, South Natick, Mass.,

USA). After heparinization (3 mg/kg), the left iliac artery and the superior mesenteric artery were isolated. A retrograde cannula was introduced into the iliac artery and connected to the circuit tubing including a heat exchanger, an occlusive roller pump, and a depulsator. Autologous blood maintained at 37 °C was pumped at a constant flow into the isolated superior mesenteric artery after cannulation and proximal ligation of the artery at its origin from the aorta (Fig. 1). A venous branch of the mesenteric vein was cannulated for blood sampling.

Perfusion pressure of the mesenteric artery was measured from the arterial line just proximal to the mesenteric inflow cannula. Perfusion flow to the mesenteric artery was adjusted by controlling the pump speed at the beginning of each experiment to obtain a mean mesenteric perfusion pressure equal to the mean aortic pressure. Changes in mesenteric perfusion pressure thus reflected changes in mesenteric arterial resistance.

Blood samples were taken regularly throughout the experiments to measure blood pH, pO_2 and pCO_2. Blood pH was maintained between 7.3 and 7.4 by ventilation adjustments and bicarbonate infusions, as needed. Isotonic saline was administered to replace fluid losses. Systemic and mesenteric arterial pressures were recorded with strain-gauge transducers on a multichannel recorder (Grass Instruments, Quincy, Mass., USA). Drugs were injected directly into the mesenteric arterial inflow, proximal to the insertion of the mesenteric artery cannula and to the site of pressure monitoring. Drugs were injected over a period of 10 min, and changes in perfusion pressure were recorded throughout the infusion period.

Nitroglycerin (5 mg in 55 ml isotonic saline) was injected into the mesenteric artery at the beginning and at the end of each experiment to test the reactivity of the mesenteric vascular bed. Pure powder CyA (Sandoz Canada, Montreal) was dissolved in autologous blood (60 ml) and injected. Autologous blood alone was also injected to test reactivity to the vehicle. At the end of each CyA infusion, blood samples from the mesenteric vein were obtained to determine CyA blood levels using the fluorescent polarization immunoassay technique [14].

To study the dose-dependent effect of CyA on the mesenteric artery, injections of four different doses of CyA (5, 10, 20 and 40 mg) into the mesenteric arterial inflow were performed in nine dogs. In another group of six dogs, the effect of blockade of alpha-adrenergic receptors by injection of phentolamine (20 mg) was studied. Norepinephrine (4 μg) was given before and after phentolamine to test the completeness of alpha-adrenergic blockade. A single 20-mg dose of CyA was administered to these animals. Typically, the mesenteric perfusion pressure reached a plateau 5–9 min after the beginning of the CyA infusion and this persisted for 5 min or more after the end of the injection. This plateau was taken as the maximal effect of the drug on mesenteric vessels. In a group of five dogs, 10 mg of CyA was injected into a systemic vein for a period of 60 min and changes in mesenteric perfusion pressure were recorded.

The data are presented as mean ± standard error of the mean (SEM) and 95 % confidence interval (CI). Changes in perfusion pressure were compared using Student's paired *t*-test. Comparisons between multiple groups were made by an analysis of variance using Fischer's exact test for intergroup comparisons. The level of statistical significance was established at 95 %. All animals were treated in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

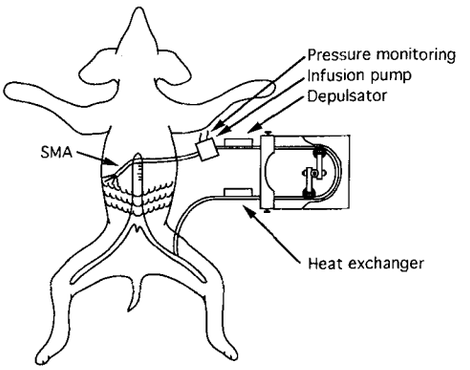

Fig. 1. Technique of isolated perfusion of the mesenteric artery in dogs. Autologous blood is pumped from the iliac artery through a heat exchanger and a depulsator into the isolated superior mesenteric artery *(SMA)*

Results

Effect of nitroglycerin and autologous blood

In the first group of nine dogs, the infusion of nitroglycerin before CyA injection caused an average decrease of 24 ± 3 mm Hg (95 % CI 18–30; $P < 0.05$) in mesenteric artery perfusion pressure, indicating a good reactivity of mesenteric arterial vessels. Basal perfusion pressure before nitroglycerin injection averaged 109 ± 5 mm Hg and decreased to an average of 85 ± 3 mm Hg during the injection. Infusing 60 ml of autologous blood did not cause any significant change in perfusion pressure (– 2 ± 4 mm Hg; 95 % CI – 11 to + 7; $P > 0.05$).

Vascular response to cyclosporin

In the same group of animals, injections of 5 and 10 mg of CyA directly into the mesenteric arterial inflow caused average increases of 3 ± 2 mm Hg (95 % CI – 2 to + 7) and 3 ± 3 mm Hg (95 % CI – 3 to + 9 mm Hg) in mesenteric perfusion pressure, respectively, changes that were not statistically significant ($P > 0.05$; Fig. 2). The mean CyA levels obtained from the mesenteric venous blood at the end of the injections were 466 ± 153 and 692 ± 130 nmol/l, respectively.

Direct infusion of 20 and 40 mg of CyA caused increases of 11 ± 3 mm Hg (95 % CI 3–18) and 26 ± 4 mm Hg (95 % CI 16–34), respectively, in mesenteric perfusion pressure. The mean CyA levels obtained from mesenteric venous blood at the end of infusion were 806 ± 85 and 1118 ± 89 nmol/l, respectively. The changes in mesenteric perfusion pressure and in CyA serum levels obtained at these doses of CyA were all significant ($P < 0.05$; Fig. 2).

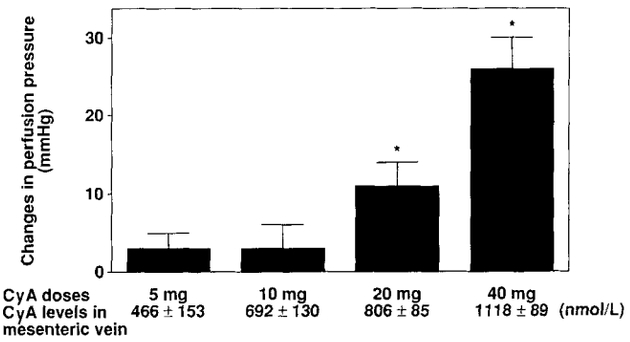

Fig. 2. Changes in mesenteric perfusion pressure (mean ± SEM) with different doses of CyA and resulting mesenteric vein serum levels. $P < 0.05$ (analysis of variance)

Effect of alpha-adrenergic blockade

In a second group of six animals, an effective blockade of alpha-adrenergic receptors with phentolamine was shown by the absence of significant vasoconstriction with the injection of 4 μg of norepinephrine (mean pressure increase of 35 ± 6 mm Hg before and 5 ± 2 mm Hg after blockade). Direct intra-arterial injection of 20 mg of CyA caused a nonsignificant change of 3 ± 3 mm Hg in mesenteric perfusion pressure after alpha-adrenergic blockade, compared to 16 ± 4 mm Hg before, a significant difference ($P < 0.05$).

Effect of systemic injections of cyclosporin

In a group of five dogs, 10 mg of CyA was injected into a systemic vein for a period of 60 min. The perfusion pressure increased from 120 ± 6 mm Hg to 132 ± 5 mm Hg during CyA infusion, an average increase of 12 ± 3 mm Hg (95 % CI 4–20; $P < 0.05$) in mesenteric perfusion pressure. The mean CyA blood levels at the end of the injections averaged 169 ± 29 nmol/l.

Discussion

Several studies have shown that CyA causes renal and femoral arterial vasoconstriction. The vasoconstriction in the renal artery is due to an increase in the local release of endothelin [1] and of thromboxane [3]. Pentoxifylline and diltiazem have been shown to be effective in preventing the vasoconstrictive effect of CyA on the renal artery [2–4]. Several authors have clearly shown that CyA also causes an increase in systemic peripheral vascular resistance through activation of the sympathetic adrenergic system [6, 9, 11, 15]. This is supported by experimental evidence in the dog indicating that CyA causes an increase in hind limb vascular resistance mediated by the sympathetic nervous system and adrenergic receptors. In addition, CyA potentiates the vasoconstriction secondary to norepinephrine by inhibition of norepinephrine re-uptake at peripheral nerve endings [15].

The effect of CyA on other arterial vessels, particularly the mesenteric artery, has never been thoroughly evaluated. The mesenteric artery is a highly catecholamine-reactive muscular artery and it is an important vessel in the regulation of systemic vascular tone [5]. Because of the higher norepinephrine content of the mesenteric artery, it was hypothesized that CyA would cause a dose-dependent vasoconstriction mediated by adrenergic receptors. The present study has effectively shown that direct infusion of CyA causes a dose-dependent increase in mesenteric vascular resistance (Fig. 2). This is mediated by adrenergic receptors, since blockade of the alpha receptor was highly effective in preventing the vascular mesenteric response to CyA. Moreover, systemic injections of CyA also caused a significant increase in mesenteric perfusion pressure at modest blood levels.

It has been reported that CyA affects bowel function by reducing glucose and fatty acid uptake in the rat [12, 13]. In humans, nonocclusive mesenteric ischemia in a renal transplant patient on CyA treatment has been well documented by Halldorsson et al. [7]. In the latter case, withdrawal of CyA resulted in the disappearance of the clinical evidence of mesenteric ischemia. It is postulated that the mesenteric vasoconstriction caused by CyA could play a significant role in the bowel dysfunction and mesenteric ischemia occasionally seen after transplantation in patients treated with CyA. In addition, it could also be involved in the hepatic dysfunction caused by CyA toxicity, since the liver is part of the mesenteric regional bed. It is noteworthy that, in our model, the mesenteric vasoconstriction was observed only when CyA levels in the mesenteric vein reached levels considered to be toxic in clinical practice. Yet, systemic injections of CyA over a longer period of time, during which sympathetic reflexes were activated, also caused mesenteric vasoconstriction at lower blood levels of CyA.

In conclusion, CyA, infused directly into the mesenteric artery, causes a dose-dependent increase in mesenteric vascular resistance, which is mediated by alpha-adrenergic receptors. This response, observed after CyA injections, may be involved in the toxic effect of the drug on the digestive tract and liver.

References

1. Carrier M, Tronc F, Stewart D, Pelletier LC (1991) Dose-dependent effect of cyclosporin on renal arterial resistance in dogs. Am J Physiol 261 (Heart Circ Physiol 30): H1791–H1796
2. Carrier M, Perreault LP, Tronc F, Stewart DJ, Pelletier CL (1993) Pentoxifylline decreases cyclosporin-induced renal endothelin release and vasoconstriction. Ann Thorac Surg 55: 490–492
3. Carrier M, Tronc F, Pelletier LC, Latour JG (1993) Role of thromboxane and angiotensin in cyclosporine-induced renal vasoconstriction in the dog. J Heart Lung Transpl 12: 851–855
4. Carrier M, Tronc F, Stewart D, Nattel S, Pelletier LC (1993) Blockade of cyclosporine-induced vasoconstriction by the calcium channel blocker diltiazem in dogs. J Thorac Cardiovasc Surg 106: 487–490
5. Colucci WS, Gimbrone MA, Alexander RW (1981) Regulation of the postsynaptic alpha-adrenergic receptor in rat mesenteric artery. Effects of chemical sympathectomy and epinephrine treatment. Circ Res 48: 104–111
6. Golub MS, Berger ME (1987) Direct augmentation by cyclosporin A of the vascular contractile response to nerve stimulation. Hypertension 9 [Suppl III]: III-96–III-100
7. Halldorsson A, Hunter GS, Zukoski CF, Putnam CW (1991) The possible role of cyclosporine in nonocclusive mesenteric ischemia in a renal transplant patient. Transplantation 51: 1298–1301
8. Kirk A, Omar I, Bateman DN, Dark JH (1989) Cyclosporin associated hypertension in cardiopulmonary transplantation. Transplantation 48: 428–430
9. Morgan BJ, Lyson T, Scherrer U, Victor RG (1991) Cyclosporine causes sympathetically mediated elevations in arterial pressure in rats. Hypertension 18: 458–460
10. Myers BD, Ross J, Newton L, Luetscher J, Perlroth M (1984) Cyclosporin associated chronic nephropathy. N Engl J Med 311: 699–705
11. Scherrer U, Vissing SF, Morgan BJ, Rollins JA, Tindall RSA, Ring S, Hanson P, Mohanty PK, Victor RG (1990) Cyclosporin-induced sympathetic activation and hypertension after heart transplantation. N Engl J Med 323: 693–699
12. Sigalet DL, Kneteman NM, Thomson ABR (1991) The effects of cyclosporine on normal bowel. Transplantation 51: 1296–1298
13. Sigalet DL, Kneteman NM, Thomson ABR (1992) Reduction of nutrient absorption in normal rats by cyclosporine. Transplantation 53: 1103–1107
14. Strassman MJ, Lensmeyer GL, Wiebe DA, Carison IH (1990) Three commercial polyclonal immunoassays for cyclosporin in whole blood compared: results with patients specimens. Clin Chem 36: 115–118
15. Tronc F, Carrier M, Pelletier CL (1992) Mechanism of hind limb vasoconstriction due to cyclosporin A in the dog. Circ Res 71: 1159–1164