British Journal of Pharmacology (1998) 125, 1247–1251
http://www.stockton-press.co.uk/bjp

Venous versus arterial actions of diethylamine/nitric oxide (DEA/NO) complex and S-nitroso-N-acetylpenicillamine (SNAP) *in vivo*

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1 We studied the effects of diethylamine/NO complex (DEA/NO) and S-nitroso-N-acetylpenicillamine (SNAP), relative to those of sodium nitroprusside (SNP) and nitroglycerin (NTG), on mean arterial pressure (MAP), mean circulatory filling pressure (MCFP), arterial resistance (R_a), venous resistance (R_v), heart rate (HR), cardiac output (CO) and stroke volume (SV) in groups of Inactin-anaesthetized rats pre-treated with i.v. mecamylamine (3.7 μmol kg^{-1}) and noradrenaline (6.8 nmol kg^{-1} min^{-1}). Doses of each that reduced MAP by 30%, 80% and the lowest dose that maximally reduced MAP were examined to allow a comparison of the compounds' dilator actions at equivalent effective depressor doses.

2 DEA/NO (4, 32 and 256 μg kg^{-1} min^{-1}), SNAP (4, 32 and 256 μg kg^{-1} min^{-1}) and SNP (8, 32 and 128 μg kg^{-1} min^{-1}) caused similar dose-dependent reductions in MAP and R_a, and increases in CO and SV. NTG (0.2, 0.8 and 6.4 μg kg^{-1} min^{-1}) dose-dependently reduced R_a, and increased CO and SV, but lowered MAP only at the highest dose.

3 DEA/NO, SNAP and SNP but not NTG lowered MCFP with efficacy: DEA/NO > SNAP > SNP. All four drugs reduced R_v with efficacy: DEA/NO $\approx$ SNAP > SNP $\approx$ NTG.

4 Therefore, all compounds lowered R_a and R_v. DEA/NO, SNAP and SNP but not NTG reduced MCFP. The pharmacological profiles of DEA/NO and SNAP resemble SNP more than NTG.

Keywords: NO/nucleophile complex; S-nitrosothiol; sodium nitroprusside; nitroglycerin; capacitance vessels; mean circulatory filling pressure; venous resistance

Introduction

Nitrovasodilators have been used for many decades in the management of cardiovascular disorders. Although the scientific literature reported the existence of at least 30 classes of nitric oxide (NO) donors, only sodium nitroprusside (SNP) and the organic nitrates (e.g., nitroglycerin, NTG) are in common clinical use (Young, 1997); the former is for lowering blood pressure in hypertensive emergencies and the latter is for the management of angina pectoris. The release of NO from SNP is believed to be spontaneous, whereas that from NTG and other organic nitrates requires the presence of thiols (e.g., cysteine and glutathione) and/or enzymatic cleavage (Harrison & Bates, 1993). It is well-documented that SNP and NTG have differential effects on the arterial and venous vasculatures. SNP efficaciously dilates both capacitance and resistance vessels. NTG, on the other hand, preferentially dilates veins to arterioles. Both drugs have drawbacks: cyanide toxicity and drug tolerance remain a concern with prolonged administration of SNP and NTG, respectively.

The undesirable pharmacological actions of the clinically available nitrovasodilators have fuelled the continuous development of new NO donors. S-nitroso-N-acetylpenicillamine (SNAP), a prototype of S-nitrosothiols, was shown to cause similar decreases in systemic arterial pressure and vascular resistance relative to SNP and NTG following i.v. injections into anaesthetized cats (Ignarro *et al*., 1981). Recently, diethylamine/NO complex (DEA/NO), a NO donor which belongs to the novel class of compounds known as the nucleophile/NO adducts that could spontaneously release NO (Maragos *et al*., 1991), was reported to cause comparable reductions in blood pressure and systemic arterial resistance as did SNP and NTG in anaesthetized rabbits (Diodati *et al*., 1993) and conscious lambs (Vanderford *et al*., 1994). There are no reports on the *in vivo* venous versus arterial pharmacological profiles of DEA/NO and SNAP.

The venous system plays a crucial role in regulating cardiac output through alterations in venous resistance and mean circulatory filling pressure which is the driving force of venous return (see Tabrizchi & Pang, 1992; Rothe, 1993; Pang, 1994). Venodilatation unequivocally contributes to the therapeutic effectiveness of SNP and NTG. This study concurrently investigated the arterial and venous actions of DEA/NO and SNAP relative to those of SNP and NTG in anaesthetized rats. To disclose the venodilator action of the drugs, the rats were ganglion-blocked and infused continuously with noradrenaline to elevate venomotor tone.

Methods

Surgery and instrumentation

Male Sprague-Dawley rats, weighing 400–500 g, were anaesthetized with Inactin (100 mg kg^{-1} i.p.). Body temperature was maintained at 37 $\pm$ 1°C with a rectal probe and a heat lamp attached to a Thermistemp Temperature Controller (Model 71; Yellow Spring Instrument Co. Inc. OH, U.S.A.). A polyethylene (PE50) catheter was introduced into the left iliac artery to record mean arterial pressure (MAP) *via* a pressure transducer (P23DB, Gould Statham, CA, U.S.A.). Heart rate

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(HR) was derived electronically from the upstroke of the arterial pulse pressure by a Grass 7P4G tachograph. Additional catheters were implanted into the left ventricle *via* the right carotid artery and the right iliac artery for the injection of radioactively-labelled microspheres and the withdrawal of a reference arterial blood sample (Wang *et al*., 1995), respectively. The vehicle or drugs were administered through cannulae inserted into the right iliac vein and the left external jugular vein. The inferior vena cava was also cannulated *via* the left iliac vein to measure central venous pressure (CVP) by another pressure transducer (P23DB, Gould Statham). A saline-filled, balloon-tipped catheter was advanced into the right atrium through the right external jugular vein. The correct positioning of the balloon was tested by transiently inflating the balloon, which when correctly placed, resulted in a simultaneous decrease in MAP to 20–25 mmHg and an increase in CVP within 5 s of circulatory arrest. MAP, HR and CVP were continuously monitored and displayed on a Grass Polygraph (Model RPS 7C8). The rats were given 30 min to stabilize before baseline values of MAP, HR, MCFP, and cardiac output (CO) were obtained.

The method for determining MCFP has been described elsewhere in detail (Tabrizchi & Pang, 1992; Wang *et al*., 1995). Briefly, steady-state readings of MAP and CVP were noted at 4–5 s after inflation of the atrial balloon. To avoid rapid equilibration of arterial and venous pressures during circulatory arrest, the arterial pressure contributed by the small amount of trapped arterial blood was corrected by the following equation: MCFP = VPP + 1/60 (FAP-VPP), where FAP and VPP denote the final arterial pressure and venous plateau pressure, respectively, and 1/60 represents the ratio of arterial to venous compliance.

Measurement of cardiac output

A well-stirred suspension (100 μl) containing 20,000–25,000 microspheres (15 μm diameter), labelled with Cobalt-57 (Du Pont Canada Inc., Ont., Canada), was injected and flushed over 10 s into the left ventricle at the end of the 30 min-equilibration period and 8 min after the i.v. infusion of a drug or vehicle. At 10 s before the injection of each set of microspheres, a blood sample was withdrawn (Harvard infusion/withdrawal pump) from the right iliac arterial cannula into a heparinized saline-filled syringe at 0.35 ml min^{-1} for 45 s. The blood removed was slowly injected back to the rats immediately after the counting of radioactivity at 80–160 keV using a 1185 Series Dual Channel Automatic Gamma Counter (Nuclear-Chicago, IL, U.S.A.) with a 3 inch NaI crystal.

Experimental protocol

Rats were randomly assigned to five groups ($n = 6$ each). Immediately after baseline measurements of haemodynamic parameters, all groups of rats were given i.v. bolus injections of mecamalyamine (3.7 μmol kg^{-1}) followed by i.v. infusion of noradrenaline (6.8 nmol kg^{-1} min^{-1}) at 10 min later. After another 10 min, each group of rats were infused with either the vehicle (0.9% NaCl), DEA/NO (4, 32 and 256 μg kg^{-1} min^{-1}), SNAP (4, 32 and 256 μg kg^{-1} min^{-1}), SNP (8, 32 and 128 μg kg^{-1} min^{-1}) or NTG (0.2, 0.8 and 6.4 μg kg^{-1} min^{-1}) for 10 min each dose. In our preliminary studies, dose-response curves were constructed for the four nitrovasodilators under similar experimental conditions (data not shown). The doses of each drug which reduced MAP by 30% (ED_{30}) and 80% (ED_{80}) from their respective maximums and the lowest dose that maximally reduced MAP (ED_{100}) were selected for the present study. CO followed by MCFP measurements were taken 8 min after the infusion of a drug or vehicle, at the plateau phase of response to each drug. A recovery period of 5 min, during which infusion was stopped, was allowed between doses. The dose of mecamylamine used was found to block ganglionic transmission effectively for more than 2 h (Wang & Pang, 1991).

Drugs

Diethylamine/nitric oxide complex sodium (DEA/NO), S-nitroso-N-acetylpenicillamine (SNAP) and Inactin were obtained from Research Biochemicals International (MA, U.S.A.). Mecamylamine hydrochloride and noradrenaline hydrochloride were purchased from Sigma Chemical Co. (MO, U.S.A.). Sodium nitroprusside (SNP) was obtained from Fisher Scientific Co. (NJ, U.S.A.). All drugs were dissolved in normal saline (0.9% NaCl) and prepared fresh daily. Nitroglycerin injection USP (NTG) was purchased from David Bull Laboratories Pty. Ltd. (Victoria, Australia) and diluted with 0.9% NaCl before use.

Calculations and data analysis

Cardiac output (CO, ml min^{-1}), stroke volume (SV, ml $beat^{-1}$), arterial resistance (R_a, mmHg min ml^{-1}) and venous resistance (R_v, mmHg min ml^{-1}) were calculated according to the following equations:

$$CO = \frac{\text{rate of withdrawal of blood} \times \text{total injected c.p.m.}}{\text{c.p.m. in withdrawn blood}}$$

$$SV = \frac{CO}{HR}$$

$$R_a = \frac{MAP}{CO}$$

$$R_v = \frac{MCFP - CVP}{CO}$$

Due to the technical difficulty of monitoring right atrial pressure in small animals, CVP rather than right atrial pressure was used to estimate pressure gradient to venous return (MCFP-right atrial pressure). This is legitimate as mean CVP is nearly identical to mean right atrial pressure (Rothe, 1993).

All results are presented as mean ± s.e.mean. Comparisons were made with analysis of variance/covariance followed by Duncan's multiple range test, with $P < 0.05$ as the criterion for statistical significance. Profile/trend analysis (curve analysis) was used to compare dose-dependency of responses with the statistical package, SYSTAT v. 5.03 (SYSTAT Inc., IL, U.S.A.) (see Wang *et al*., 1995).

Results

Table 1 shows the values (means ± s.e.mean) of haemodynamic variables for the five groups of rats at baseline, at steady-state response to i.v. bolus injections of mecamylamine (3.7 μmol kg^{-1}) and to i.v. infusion (6.8 nmol kg^{-1} min^{-1}) of noradrenaline. Baseline values of MAP, CO, SV, HR, MCFP, R_a and R_v were not significantly different among the five groups. Intravenous bolus injections of mecamylamine reduced MAP, HR, CO, SV and MCFP, but did not significantly alter R_a and R_v. The subsequent infusion of noradrenaline significantly increased MAP, HR, MCFP, R_a and R_v, but did not change CO and SV. Therefore, the combination of

Table 1 Values (means ± s.e.mean) of mean arterial pressure (MAP), cardiac output (CO), heart rate (HR), mean circulatory filling pressure (MCFP), arterial resistance (R_a) and venous resistance (R_v) for the five groups ($n=6$ each) of rats at baseline, at steady-state response to i.v. bolus injections of mecamylamine (3.7 μmol kg^{-1}) and i.v. noradrenaline infusion (6.8 nmol kg^{-1} min^{-1}) are presented in the first, second and third row, respectively

	Vehicle	*DEA/NO*	*SNAP*	*SNP*	*NTG*
MAP	92 ± 2	91 ± 2	91 ± 3	95 ± 2	93 ± 3
(mmHg)	66 ± 4[a]	63 ± 3[a]	68 ± 3[a]	69 ± 2[a]	66 ± 4[a]
	110 ± 3[a,b]	109 ± 3[a,b]	119 ± 4[a,b]	117 ± 5[a,b]	112 ± 3[a,b]
CO	95 ± 6	97 ± 6	90 ± 3	93 ± 4	101 ± 7
(ml min^{-1})	75 ± 5[a]	77 ± 8[a]	69 ± 7[a]	77 ± 3[a]	76 ± 4[a]
	70 ± 4[a]	58 ± 6[a]	57 ± 5[a]	67 ± 4[a]	68 ± 5[a]
HR	362 ± 10	359 ± 11	348 ± 9	363 ± 12	375 ± 14
(beats min^{-1})	329 ± 7[a]	325 ± 12[a]	320 ± 6[a]	328 ± 8[a]	345 ± 12[a]
	403 ± 9[a,b]	387 ± 15[a,b]	402 ± 6[a,b]	415 ± 10[a,b]	393 ± 15[a,b]
SV	0.264 ± 0.019	0.272 ± 0.016	0.259 ± 0.010	0.259 ± 0.013	0.270 ± 0.015
(ml beat^{-1})	0.228 ± 0.14[a]	0.239 ± 0.025[a]	0.216 ± 0.019[a]	0.236 ± 0.011[a]	0.224 ± 0.016[a]
	0.174 ± 0.012[a]	0.154 ± 0.018[a]	0.141 ± 0.010[a]	0.162 ± 0.010[a]	0.175 ± 0.013[a]
MCFP	3.9 ± 0.3	4.1 ± 0.2	3.7 ± 0.2	3.8 ± 0.2	4.0 ± 0.3
(mmHg)	3.1 ± 0.2[a]	3.3 ± 0.1[a]	2.9 ± 0.2[a]	3.2 ± 0.3[a]	3.0 ± 0.2[a]
	5.3 ± 0.4[a,b]	5.9 ± 0.3[a,b]	5.3 ± 0.2[a,b]	5.4 ± 0.5[a,b]	4.9 ± 0.4[a,b]
R_a	0.98 ± 0.04	0.95 ± 0.05	1.02 ± 0.04	1.02 ± 0.03	0.94 ± 0.06
(mmHg min ml^{-1})	0.88 ± 0.04	0.86 ± 0.06	1.02 ± 0.09	0.90 ± 0.04	0.82 ± 0.07
	1.60 ± 0.09[a,b]	2.02 ± 0.30[a,b]	2.21 ± 0.26[a,b]	1.78 ± 0.13[a,b]	1.65 ± 0.12[a,b]
R_v	0.030 ± 0.004	0.032 ± 0.002	0.030 ± 0.003	0.030 ± 0.002	0.031 ± 0.004
(mmHg min ml^{-1})	0.028 ± 0.002	0.032 ± 0.004	0.030 ± 0.005	0.028 ± 0.003	0.026 ± 0.002
	0.061 ± 0.006[a,b]	0.090 ± 0.011[a,b]	0.080 ± 0.008[a,b]	0.066 ± 0.007[a,b]	0.057 ± 0.004[a,b]

[a]Significantly ($P<0.05$) different from the corresponding baseline readings prior to any drug treatment. [b]Significantly ($P<0.05$) different from the corresponding readings after mecamylamine injection.

ganglionic blockade and noradrenaline, relative to the corresponding pre-treatment baselines, increased MAP, HR, MCFP, R_a and R_v but decreased CO and SV.

The vehicle (time-control) did not significantly alter any of the haemodynamic parameters (Figures 1 and 2). DEA/NO, SNAP, SNP and NTG caused similar dose-dependent increments in CO and SV, but had no significant effects on HR at all three doses (Figure 1). MAP was dose-dependently and similarly reduced by DEA/NO, SNAP and SNP. NTG did not significantly lower MAP except at the highest dose (Figure 1). While DEA/NO, SNAP, SNP and NTG elicited comparable reductions in R_a at the ED_{30} doses, DEA/NO, SNAP and SNP caused greater reductions in R_a than did NTG at higher doses (Figure 2). Curve analysis revealed that DEA/NO, SNAP and SNP caused significantly greater reductions of R_a than did NTG. The onset and duration of action of the four nitrovasodilators were rapid (within s) and short, respectively, as MAP returned to predrug level soon after the infusion was terminated (data not shown).

Resting CVP values varied from 0.5 – 1.5 mmHg among the five groups of rats and were not altered by any of the nitrovasodilators. DEA/NO, SNAP and SNP dose-dependently lowered MCFP, whereas NTG did not alter MCFP at any dose (Figure 2). Curve analysis demonstrated that DEA/NO caused greater reductions of MCFP than did SNP and SNAP. DEA/NO, SNAP, SNP and NTG caused dose-dependent reductions in R_v (Figure 2). Curve analysis showed that the effects of DEA/NO and SNAP on R_v were greater than those of SNP and NTG.

Discussion

Our results show that i.v. infusions of DEA/NO and SNAP, similar to SNP, caused dose-dependent reductions in MAP and R_a, and increases in CO and SV. Thus, all three drugs lowered blood pressure by decreasing arteriolar resistance. I.V. infusion of NTG dose-dependently decreased R_a, and increased CO and SV, but did not significantly reduce MAP except at the highest dose. Curve analysis illustrated that the arteriolar dilator effects of NTG were significantly less than those of DEA/NO, SNAP and SNP. The inability of i.v. infused NTG to reduce MAP is therefore a consequence of its lesser arteriolar dilator action.

HR was not affected by any drugs. Since the rats were ganglion-blocked with mecamylamine, the lack of effects on HR indicates that these drugs do not have any direct chronotropic action.

In accord with our findings, Diodati *et al*. (1993) demonstrated that DEA/NO was equipotent to SNP in lowering MAP and systemic vascular resistance in anaesthetized rabbits, although neither DEA/NO nor SNP affected CO. DEA/NO (1.5 and 2.0 μg kg^{-1} min^{-1}) has also been reported to decrease MAP and systemic vascular resistance without altering HR or CO in intact newborn lambs (Vanderford *et al*., 1994). Contrary to our results, the Vanderford study showed that SNP reduced MAP more than did DEA/NO, SNAP and NTG during U46619-induced pulmonary hypertension. Differences among the various studies could be due to variations in species, doses, modes of drug administration and experimental conditions.

Since the venodilator activity of a drug is best revealed in animals with inactivation of the sympathetic nervous system and/or elevation of venomotor tone (Tabrizchi & Pang, 1992; Pang, 1994), the rats in this study were given mecamylamine to suppress autonomic reflex and infused with noradrenaline to elevate venomotor tone. Under these conditions, DEA/NO, SNAP as well as SNP dose-dependently reduced MCFP. NTG, however, did not alter MCFP at any dose. Curve analysis revealed that the reductions of MCFP by DEA/NO were significantly greater than those produced by SNP and SNAP.

All four drugs lowered R_v relative to the vehicle, with no significant differences among groups at the ED_{30} and ED_{80}

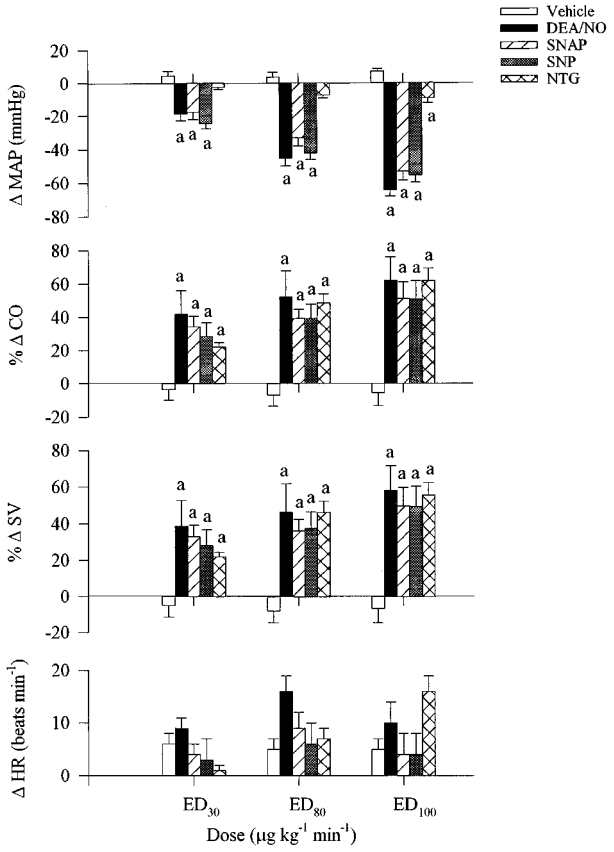

Figure 1 Effects (mean ± s.e.mean) of i.v. infusion of DEA/NO (4, 32 and 256 μg kg^{-1} min^{-1} shown as effective depressor doses, ED_{30}, ED_{80} and ED_{100}, respectively), SNAP (4, 32 and 256 μg kg^{-1} min^{-1}), SNP (8, 32 and 128 μg kg^{-1} min^{-1}), NTG (0.2, 0.8 and 6.4 μg kg^{-1} min^{-1}) or equivalent volumes of vehicle (0.9% NaCl) on mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV) and heart rate (HR) in five groups of rats ($n=6$ each) pre-treated i.v. with mecamylamine (3.7 μmol kg^{-1}) and noradrenaline (6.8 nmol kg^{-1} min^{-1}). All measurements were obtained 8 min after the infusion of a drug or vehicle. [a]Significantly different ($P<0.05$) from the corresponding values in the vehicle group.

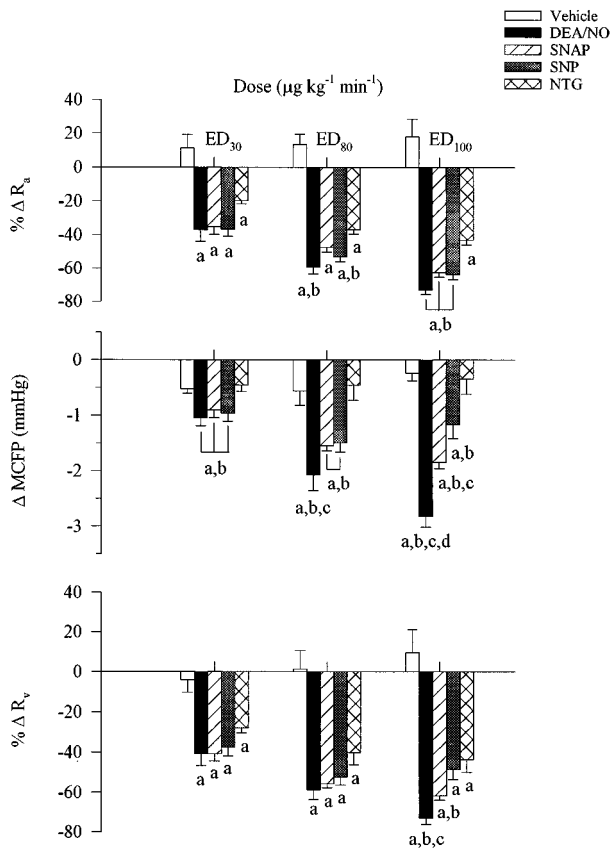

Figure 2 Effects (mean ± s.e.mean) of DEA/NO (4, 32 and 256 μg kg^{-1} min^{-1} shown as effective depressor doses, ED_{30}, ED_{80} and ED_{100}, respectively), SNAP (4, 32 and 256 μg kg^{-1} min^{-1}), SNP (8, 32 and 128 μg kg^{-1} min^{-1}), NTG (0.2, 0.8 and 6.4 μg kg^{-1} min^{-1}) or equivalent volumes of vehicle (0.9% NaCl) on arterial resistance (R_a), mean circulatory filling pressure (MCFP) and venous resistance (R_v) in five groups of rats ($n=6$ each) pre-treated with i.v. mecamylamine (3.7 μmol kg^{-1}) and noradrenaline (6.8 nmol kg^{-1} min^{-1}). All measurements were obtained 8 min after the infusion of a drug or vehicle. [a]Significantly different ($P<0.05$) from the corresponding values in the vehicle group. [b]Significantly different ($P<0.05$) from the corresponding values in the NTG group. [c]Significantly different ($P<0.05$) from the SNP group. [d]Significantly different ($P<0.05$) from the SNAP group.

doses but significantly greater reductions of R_v by the highest doses of DEA/NO and SNAP. Curve analysis showed the reductions in R_v were greater for DEA/NO and SNAP than SNP and NTG. Our results indicate that DEA/NO is the most efficacious venodilator agent among the four tested compounds. The differences in venodilatation elicited by the four NO donors may be attributed to the differences in the amount and/or rate of NO released from these agents. Using a chemiluminescence technique to monitor NO evolution, Morley *et al* (1993) demonstrated that both DEA/NO and SNAP spontaneously released NO, whereas SNP and NTG generated negligible NO under similar conditions. The release of NO from DEA/NO was shown to be controlled and predictable, in sharp contrast to the erratic release from SNAP. In fact, it has been shown that the NO-generating activity of SNAP might also involve a metabolic activation step similar to that of NTG, in addition to spontaneous release (Kowaluk & Fung, 1990). The differential mechanisms of NO release, which in turn, determine the amount and rate of NO released from these compounds, may in part account for their differential venodilating potencies and efficacies. We could not explain why these differences were not manifested in the arterial vasculature. It is possible that capacitance vessels may be more sensitive than resistance vessels to small variations of NO concentration *in situ*.

CO was similarly increased by all four compounds. The increases in CO were the result of reduced flow resistance, R_a as well as R_v. In the absence of HR changes, CO elevations were entirely due to increments in SV, consistent with the Frank–Starling mechanism.

We conclude that DEA/NO and SNAP produced similar dose-dependent increases in CO and SV as did SNP and NTG, similar reductions in MAP and R_a as SNP, and more reductions in MAP and R_a relative to NTG. DEA/NO, SNAP and SNP but not NTG lowered MCFP with the following rank order of efficacy: DEA/NO > SNAP > SNP. All four drugs reduced R_v, with the following efficacy: DEA/NO $\approx$ SNAP > SNP $\approx$ NTG. Our results indicate that DEA/NO is a more efficacious venodilator than SNAP, SNP and NTG. The pharmacological profiles of DEA/NO and SNAP resemble more closely to those of SNP than NTG.

This work was supported by the Heart and Stroke Foundation of BC and Yukon, Canada. S.S.W. Ng was a recipient of the University of British Columbia Graduate Fellowship award.

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(Received December 23, 1997
Revised July 15, 1998
Accepted August 19, 1998)