Br. J. Pharmac. (1978), **62**, 143–146

EFFECTS OF MINOXIDIL AND NITROPRUSSIDE ON REFLEX INCREASES IN MYOCARDIAL CONTRACTILITY

N.W. ROBIE

Department of Pharmacology, Louisiana State University Medical Center, 1100 Florida Avenue, New Orleans, Louisiana 70119, U.S.A.

1 The effects of nitroprusside and minoxidil on increases in myocardial contractility resulting from carotid artery occlusion were investigated in anaesthetized dogs. The results were compared with those produced by intravenous influsion of noradrenaline.

2 Nitroprusside and minoxidil attenuated the pressor responses produced by carotid artery occlusion.

3 Nitroprusside, but not minoxidil, attenuated the maximal myocardial contractility resulting from carotid occlusion.

4 The pressor and contractility responses to noradrenaline infusion were unaffected by either agent.

5 Nitroprusside failed to alter the myocardial responses produced by dimethylphenylpiperazinium.

6 These results, in conjunction with those of other investigators who have demonstrated that nitroprusside does not affect the release of noradrenaline from adrenergic neurones, suggest that nitroprusside may inhibit sympathetic nervous system reflex activity via an afferent and/or central component.

Introduction

The cardiovascular effects of sodium nitroprusside and minoxidil have been well documented and attributed to a generalized relaxation of vascular smooth muscle. However, there are still unanswered questions concerning the effects of these drugs on sympathetic nervous system function. DuCharme, Freyburger, Graham & Carlson (1973) reported that minoxidil attenuated the pressor response to carotid occlusion as well as the vasoconstrictor response evoked by electrical stimulation of sympathetic nerves in the hind limb of the dog. However, responses dependent upon vascular constriction should be interpreted with caution, since vasodilator drugs may impair or prevent maximal contractile responsiveness. Further, a review of the literature did not reveal studies describing the effect of nitroprusside on sympathetic nervous system function. Therefore, the following experiments were performed to evaluate the effects of minoxidil and nitroprusside on reflex changes in myocardial contractility produced by carotid occlusion and to compare these changes with those produced by exogenous noradrenaline.

Methods

Six mongrel dogs of either sex were anaesthetized with pentobarbitone sodium (30 mg/kg i.v.). Following bilateral vagotomy, two brachial veins and an artery were cannulated for infusion of drugs and measurement of mean arterial pressure with a Statham P23D pressure transducer. A catheter was advanced into the left ventricle via the left common carotid artery for measurement of left ventricular pressure. The maximum rate of rise of ventricular pressure (dP/dt) was obtained with an active operational amplifier circuit. Myocardial contractility was determined as the instantaneous dP/dt (mmHg/s) at developed pressure of 40 mmHg, thus eliminating influences of pre- and after-load. Heart rate was measured with a cardiotachometer.

The protocol consisted of measuring the above parameters during (1) control period; (2) one minute carotid artery occlusion (right common carotid); and (3) three 10 min infusions of (−)-noradrenaline at doses of 0.1, 0.2 and 0.4 $\mu g\ kg^{-1}min^{-1}$. These three procedures were carried out during (1) no drug (ND); (2) nitroprusside infused at a rate sufficient to decrease mean arterial pressure to approximately 85 mmHg (dose range, 8–32 $\mu g\ kg^{-1}min^{-1}$); and (3) following recovery from nitroprusside, 1.5–2.0 h after minoxidil 2 mg/kg intravenously. To allow for autoregulatory circulatory adjustments, nitroprusside was infused for 20 min before the three procedures outlined above were performed. Owing to the long duration of the effect of minoxidil, the order of drug administration was not reversed.

In another series of experiments, three dogs were anaesthetized with pentobarbitone (30 mg/kg i.v.), vagotomized and cannulated for measurement of arterial pressure. Following institution of positive pressure respiration, a right thoracotomy was performed and a Walton-Brodie strain gauge arch sutured to the right ventricle for measurement of changes in contractile force. The animals were then given atropine 2 mg/kg intravenously. After stable base lines were obtained, dimethylphenylpiperazinium (DMPP) was injected intravenously at doses of 3, 6, and 10 μg/kg. Nitroprusside was then infused at a rate of 5 $\mu g\ kg^{-1}min^{-1}$ for 10 min, and the DMPP injections were repeated during the nitroprusside infusion.

The data are expressed as mean $\pm$ 1 standard error of the mean, and statistical analyses were performed using Student's t test.

Drugs used were: sodium nitroprusside, (−)-noradrenaline bitartrate, atropine sulphate (Sigma Chemical Co.), minoxidil (kindly supplied by the Upjohn Company), and 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP; Aldrich Chemical Co., Inc.). All doses are expressed as weight of the free radical.

Results

The results are summarized in Table 1. Nitroprusside and minoxidil produced equivalent depressor effects, decreasing mean arterial pressure ($P < 0.01$) from 132 $\pm$ 7 mmHg to 85 $\pm$ 4 and 80 $\pm$ 7 mmHg, respectively. The difference in pressor response during carotid artery occlusion was less ($P < 0.05$) for nitroprusside (28 $\pm$ 8 mmHg) and minoxidil (27 $\pm$ 10 mmHg) than during ND (56 $\pm$ 5 mmHg), and the responses observed during treatment with nitroprusside and minoxidil were not different from each other. Conversely, when compared to ND, neither nitroprusside nor minoxidil significantly reduced the incremental responses produced by noradrenaline infusion, although the absolute values are naturally lower than those observed during ND. However, the pressor response to the infusion of noradrenaline 0.4 $\mu g\ kg^{-1}min^{-1}$ was attenuated by minoxidil when compared to nitroprusside ($P < 0.05$).

Heart rate increased ($P < 0.01$) from control (167 $\pm$ 4 beats/min) to 195 $\pm$ 9 beats/min and 193 $\pm$ 9 beats/min in response to nitroprusside and minoxidil, respectively. Carotid artery occlusion increased heart rate during ND ($P < 0.001$), but did not change the heart rate during administration of nitroprusside or minoxidil. Noradrenaline, 0.4 $\mu g\ kg^{-1}min^{-1}$, increased heart rate during ND ($P < 0.02$), but did not significantly increase the heart rate during administration of nitroprusside or minoxidil.

Myocardial contractility resulting from either nitroprusside infusion or minoxidil was not statistically different from ND, but the contractility during minoxidil was greater than that observed during nitroprusside ($P < 0.05$). Carotid artery occlusion increased contractility during all three periods ($P < 0.05$). The increases observed during either nitroprusside or minoxidil treatment were significantly less than ND ($P < 0.05$). However, the maximum response obtained during minoxidil (3128 $\pm$ 328 mmHg/s) was not different from ND occlusion (3536 $\pm$ 436 mmHg/s), although the maximum during nitroprusside was significantly lower (2696 $\pm$ 320 mmHg/s). Noradrenaline produced dose-related increases in contractility that were not significantly altered by either vasodilator drug.

Table 1 Effects of carotid artery occlusion and noradrenaline infusion on mean blood pressure, heart rate and myocardial contractility during no drug (ND), sodium nitroprusside infusion (SN) and minoxidil (Mx)

Variable	*Treatment*	*Control*	*Carotid occlusion*	*Difference (occl − cont)*	*Noradrenaline ($\mu g - kg^{-1}\ min^{-1}$) 0.1*	*0.2*	*0.4*
BP (mmHg)	ND	132 ± 7	187 ± 10[a]	55 ± 5	148 ± 7[a]	160 ± 9[a]	166 ± 11[a]
	SN	85 ± 4[b]	114 ± 11[ab]	28 ± 8[b]	97 ± 3[ab]	110 ± 4[ab]	121 ± 7[ab]
	Mx	80 ± 7[b]	107 ± 16[ab]	27 ± 10[b]	86 ± 6[ab]	94 ± 6[ab]	100 ± 7[abc]
HR (beats/min)	ND	167 ± 4	186 ± 6[a]	19 ± 3	162 ± 6	166 ± 6	180 ± 4[a]
	SN	195 ± 9[b]	190 ± 10	5 − 4[b]	193 ± 6[b]	198 ± 7[b]	203 ± 8[b]
	Mx	193 ± 9[b]	192 ± 10	1 − 2[b]	196 ± 9[b]	199 ± 8[ab]	203 ± 7[b]
dP/dt (mmHg/s)	ND	2512 ± 212	3536 ± 436[a]	1028 ± 272	2726 ± 252	3408 ± 176[a]	3706 ± 231[a]
	SN	2236 ± 232	2696 ± 320[ab]	464 ± 144[b]	2564 ± 72	3100 ± 188[a]	3956 ± 188[a]
	Mx	2780 ± 188[c]	3128 ± 328[a]	353 ± 116[b]	3000 ± 236	3416 ± 200[a]	3712 ± 192[a]

BP = mean blood pressure; HR = heart rate; dP/dt = dP/dt at developed pressure of 40 mmHg; a = statistically different from control; b = statistically different from ND; c = statistically different from SN; $P < 0.05$ unless stated otherwise in text.
Results are means ± s.e. mean and were compared by Student's t test.

Analysis of dose-response data obtained from the effect of noradrenaline on blood pressure, heart rate and contractility revealed that when either nitroprusside or minoxidil were administered, the slope of the response was not different from that observed during ND.

Nitroprusside did not affect the contractile force or heart rate responses to injections of DMPP.

Discussion

Previous reports have indicated that the pressor response to carotid artery occlusion may be reduced by vasodilator agents such as hydralazine (Antonaccio, Robson & Povalski, 1973) and, in conscious dogs, minoxidil (DuCharme *et al.*, 1973). This action of minoxidil was confirmed in the present experiments with anaesthetized dogs and nitroprusside was also shown to attenuate the reflex pressor response, a finding that has not been reported previously. However, this decreased pressor response is not necessarily indicative of a decreased sympathetic nervous system activity since minoxidil and nitroprusside produce a direct relaxation of vascular smooth muscle and may thereby prevent equivalent contraction of vessels for a given stimulus.

Occlusion of the carotid artery during ND resulted in an increase in myocardial contractility intermediate between the response of the 0.2 and 0.4 $\mu g\ kg^{-1}min^{-1}$ noradrenaline. During administration of either nitroprusside or minoxidil the reflex increase in contractility was reduced to a level comparable to 0.1 $\mu g\ kg^{-1}min^{-1}$ noradrenaline. However, in the case of minoxidil, this apparent reduction in myocardial responsiveness does not necessarily indicate a decrease in reflex activity to the heart. Occlusion of the carotid arteries is generally considered to produce the maximum sympathetic stimulation that is physiologically obtainable. During minoxidil treatment, the contractile response produced by carotid occlusion was equal to or greater than that observed when no drug was given for four of the six animals studied. Since (1) the control value for minoxidil was higher than that for ND, (2) the response to carotid occlusion with ND was the maximum obtainable for such a stimulus, and (3) the value observed for carotid occlusion during minoxidil was not significantly different from the ND response, then it cannot be concluded that minoxidil attenuated the reflex activity to the myocardium.

The same argument does not apply to the decreased myocardial response to carotid occlusion during administration of nitroprusside, since not only the incremental increase but also the maximum response was significantly lower than the equivalent ND response. The reason for this reduced responsiveness is not readily apparent although several possibilities may be excluded. The decreased response in myocardial contractility clearly was not due to a direct myocardial depressant effect or β-adrenoceptor blockade, since the responses to noradrenaline were unaffected by nitroprusside. Further, Gmeiner, Riedl & Baumgartner (1975) demonstrated that nitroprusside did not directly affect contractility of the rat isolated heart. While many drugs have been shown to inhibit the release of noradrenaline (Langer, 1974; Vanhoutte, 1974; Malik & Nasjletti, 1977), this does not appear to be the case for nitroprusside. Verhaeghe & Shepherd (1976) demonstrated in isolated saphenous vein strips that nitroprusside decreased the tension produced by electrical stimulation, but did not alter the output of [^{3}H]-noradrenaline. The present study also demonstrated that nitroprusside did not alter myocardial contractile force or heart rate produced by the ganglionic stimulating agent DMPP. Thus, it appears that nitroprusside may affect the afferent and/or central components of the baroreceptor reflex mechanism.

This alteration in baroreceptor reflex mechanism for nitroprusside may be of significance in certain laboratory procedures where this agent is used. However, the clinical implication of such an effect requires further investigation.

References

ANTONACCIO, M.J., ROBSON, R.D. & POVALSKI, H.S. (1973). Modification by antihypertensive drugs of reflex circulatory responses induced by vertical tilting or bilateral carotid occlusion. *Eur. J. Pharmac.*, **22**, 23–31.

DuCHARME, D.W., FREYBURGER, W.A., GRAHAM, B.E. & CARLSON, R.G. (1973). Pharmacologic properties of minoxidil: a new hypotensive agent. *J. Pharmac. exp. Ther.*, **184**, 662–670.

GMEINER, R., RIEDL, J. & BAUMGARTNER, H. (1975). Effect of sodium nitroprusside on myocardial performance and venous tone. *Eur. J. Pharmac.*, **31**, 287–291.

LANGER, S.Z. (1974). Presynaptic regulation of catecholamine release. *Biochem. Pharmac.*, **23**, 1793–1800.

MALIK, K.U. & NASJLETTI, A. (1977). Inhibitory effect of bradykinin on vascular responses to sympathetic nerve stimulation in the isolated perfused rabbit kidney. *Fedn Proc.*, **36**, 547.

VANHOUTTE, P.M. (1974). Inhibition by acetylcholine of adrenergic neurotransmission in vascular smooth muscle. *Circulation Res.*, **34,** 317–326.

VERHAEGHE, R.H. & SHEPHERD, J.T. (1976). Effect of nitroprusside on smooth muscle and adrenergic nerve terminals in isolated blood vessels. *J. Pharmac. exp. Ther.*, **199,** 269–277.

(Received July 1, 1977.
Revised August 18, 1977.)