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The effects of B-HT 920 and St 91 on venous haemodynamics in cats

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Abstract—The present study reports the effects of 2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]azepin dihydrochloride (B-HT 920) and 2-(2,6-diethylphenylimino)-2-imidazolidine hydrochloride (St 91) in autoperfused cat hindquarters since we have previously shown that clonidine lowered blood pressure, heart rate and vena cava blood flow (VCBF) but not hindquarters perfusion pressure, indicating a selective venodilator action of this drug (Bentley et al 1986). It was found that intravenous (i.v.) and intracisternal (i.c.m.) administration of B-HT 920 caused essentially identical effects to those of clonidine. St 91, given i.c.m. lowered blood pressure and VCBF but not perfusion pressure, while i.v. St 91 had little effect on these variables. Thus, parallel changes in blood pressure and VCBF occurred using both drugs, suggesting that these centrally-acting clonidine-like drugs also caused selective venodilatation.

We have recently shown that venodilatation together with an expansion of collateral venous routes contributes to the hypotensive effect of clonidine (Bentley et al 1986). This is consistent with the repeated findings that clonidine reduces cardiac output although total peripheral resistance is less affected (see Schmitt 1977). To examine whether this haemodynamic pattern occurs with other clonidine-like drugs, the effects of 2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]azepin dihydrochloride, Boehringer Ingelheim (B-HT 920) and 2-(2,6-diethylphenylimino)-2-imidazolidine hydrochloride, Boehringer Ingelheim (St 91) were studied. B-HT 920 is a selective α_2-adrenoceptor agonist that lowers blood pressure and heart rate in cats (Pichler & Kobinger 1981), while St 91 is an analogue of clonidine that causes hypotension when administered centrally, but only bradycardia when given intravenously to animals (Hoefke et al 1975; McLennan & Bentley 1978, 1983). However, the effects of these two drugs on venous haemodynamics have not previously been described.

Materials and methods

Twenty-two cats of either sex, 3·5–5·3 kg, were used. They were anaesthetized with chloralose and set up for the measurement of arterial and venous function in cat hindquarters as previously described (Bentley et al 1986). This involved the autoperfusion of the hindquarters region via the abdominal aorta using a constant-flow perfusion pump. Hindquarter perfusion pressure, measured distal to the pump, was set to approximate systemic blood pressure, measured in the brachial artery, by adjusting blood flow to the region. A flow probe (1·5 mm i.d., Biotronex) was also placed around the inferior vena cava to measure mean vena cava blood flow (VCBF). All variables were displayed on a Grass polygraph (Model 7D). Arterial inflow delivered to the hindquarters was constant and this approximated venous outflow (i.e. VCBF) from the region (see Table 1). Thus changes in perfusion pressure reflected changes in peripheral resistance while changes in VCBF reflected changes in capacitance. B-HT 920 and St 91 were injected intravenously (i.v.) in a volume of 0·1 mL kg^{-1} or into the cisterna magna (i.c.m.) in a volume of 0·1 mL after a similar amount of cerebrospinal fluid had been removed. All concentrations refer to the base substance and only one drug was given to each animal.

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Results

The i.v. injection of either B-HT 920, 30 μg kg^{-1}, or St 91, 2 μg kg^{-1}, produced transient pressor responses in both the systemic and hindquarter circulations of approximately 60–80 mmHg and 30–40 mmHg, respectively, together with increases in VCBF of 6–8 mL min^{-1}. In the case of B-HT 920, this was followed by the hypotensive phase of the drug in which mean arterial pressure, heart rate, VCBF and, to a lesser extent PP, all decreased (Table 1). The reduction in VCBF followed a similar time course to the onset of hypotension, both of which were maximal within 5–10 min. In contrast, St 91 did not cause persistent decreases in either mean arterial pressure or VCBF (Table 1), and larger concentrations of this drug (8 and 20 μg kg^{-1}) also failed to elicit hypotension or a reduction in VCBF (data not shown).

When given by i.c.m. injection, both B-HT 920, 3 μg kg^{-1}, and St 91, 2 μg kg^{-1}, caused parallel reductions in both mean arterial pressure and VCBF without the initial sympathomimetic effects. These effects were maximal within 10–20 min, although perfusion pressure remained unaltered (Table 1).

Discussion

The results of the present study provide further evidence for the

Table 1. Changes in mean arterial pressure (MAP, mmHg), heart rate (HR, beats min^{-1}), hindquarter perfusion pressure (PP, mmHg), arterial inflow (AIn, mL min^{-1}) and mean vena cava blood flow (VCBF, mL min^{-1}) of chloralose-anaesthetized cats with autoperfused hindquarters in response to B-HT 920 and St 91 given intravenously (i.v.) or intracisternally (i.c.m.).

Treatment	Variable	Initial Value	Change	% Change
B-HT 920,	MAP	85±4·3	−31±3·9*	−36±3·5
30 μg kg^{-1}	HR	174±9·3	−25±5·8*	−15±3·9
i.v. (n=6)	PP	96±7·5	−7±1·8*	−8±1·8
	AIn	13·0±1·6	—	—
	VCBF	15·1±2·7	−3·0±0·6*	−23±5·4
B-HT 920	MAP	86±16·3	−30±8·8*	−34±5·9
3 μg kg^{-1}	HR	211±16·5	−31±8·7*	−14±3·2
i.c.m. (n=5)	PP	114±14·2	0±8·4	+1±6·9
	AIn	18·4±3·1	—	—
	VCBF	19·7±2·6	−3·0±0·4*	−16±2·4
St 91	MAP	80±5·8	−6±4·2	−6±4·6
2 μg kg^{-1}	HR	184±12·3	−17±5·7*	−10±4·6
i.v. (n=6)	PP	99±7·1	+2±2·3	+2±2·3
	AIn	17·2±2·7	—	—
	VCBF	20·3±2·5	−0·3±0·2	−1·6±1·3
St 91	MAP	87±8·2	−17±2·5*	−21±5·0
2 μg kg^{-1}	HR	193±18·1	−4±1·4	−2±0·6
i.c.m. (n=5)	PP	102±9·4	+3±2·3	+3±2·0
	AIn	17·7±2·5	—	—
	VCBF	13·8±2·2	−2·9±0·7*	−26±8·1

Data shown are means±s.e. mean during the hypotensive phase of each treatment.

+ and − indicate increases and decreases in the appropriate variable.

* Significantly different from control levels, $P < 0.05$, paired t-test.

importance of venodilatation in the hypotensive effect of centrally acting clonidine-like drugs. The reductions in blood pressure and heart rate caused by B-HT 920 when given by either route were similar to those reported in an earlier study in which this drug was also shown to inhibit spontaneous sympathetic nerve activity (Pichler & Kobinger 1981). The present experimental techniques also allowed for the simultaneous measurement of arterial and venous function in the hindquarters, the advantages of which have been discussed previously (see Bentley et al 1986). This showed that B HT 920 caused parallel changes in blood pressure and VCBF, but not perfusion pressure.

As expected, i.v. St 91 failed to lower blood pressure significantly, although when given i.c.m. hypotension did occur, in agreement with other studies (Hoefke et al 1975; McLennan & Bentley 1978, 1983). Interestingly, St 91 also consistently decreased VCBF following i.c.m. administration but not when given i.v., and there were again negligible changes in perfusion pressure. Failure of i.v. St 91 to cause hypotension is thought to be due to poor distribution of the drug within the central nervous system or possibly due to a persistent peripheral vasoconstriction which balances any central effects (Hoefke et al 1975). However, in the present study, there were only transient constrictor responses in both the arterial and venous circulations. Thus, these results show that concomitant changes in blood pressure and VCBF, but not perfusion pressure, occur following either B-HT 920 or St 91 administration, although the individual effects of these drugs were somewhat different. The haemodynamic profiles of St 91 (i.c.m.) and B-HT 920 (i.v. & i.c.m.) are essentially identical to those described following clonidine in cats (Bentley et al 1986). That is, the parallel reductions in blood pressure and VCBF persisted for 30–60 min, although arterial inflow to the region was held constant and perfusion pressure was unaffected. Therefore, this would suggest a common mechanism for all three drugs involving venodilatation and an expansion of collateral venous routes (see Bentley et al 1986). Such a venodilator action of clonidine has previously been observed in dogs (Nayler et al 1968; Bentley et al 1986) and man (Ehringer 1966; Quiroz et al 1983) and therefore could account for the lowered cardiac output known to occur after clonidine (see Introduction). The lack of any venous effect of i.v. St 91 is consistent with the absence of hypotension, although the reason for this is not clearly understood.

This apparent venoselectivity of the three drugs tested (present study; Bentley et al 1986) could occur if there was a selective reduction in venous sympathetic tone, or if a given percentage reduction in overall sympathetic tone produced a greater effect on veins than on arteries (Bentley 1987). This latter effect could be manifested either because veins have a sparser innervation or because of the mechanical properties of the more compliant, thin-walled veins (Shepherd & Vanhoutte 1975). Thus, the present findings may be explained by a selective reduction in sympathetic tone to veins and/or less reserve sympathetic function in veins than arteries that is manifested as a venoselective event.

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References

Bentley, G. A. (1987) Clonidine, A Widow's Cruse for Pharmacologists. Clin. Exp. Pharmacol. Physiol. 14: 465–470

Bentley, G. A., Cullen, L. K., Reynoldson, J. A., Widdop, R. E. (1986) The effect of clonidine on venous haemodynamics in cats and dogs. Br. J. Parmacol. 88: 161–171

Ehringer, V. H. (1966) DieWirkung von 2-(2,6-dichlorphenylamino)-2-imidazolin-hydrochlorid auf die Extremitatendurchblutung, den Blutdruck und die Venenkapazitat bie Normotonikern. Arzneimittelforsh 16: 1165–1169

Hoefke, W., Kobinger, W., Walland, A. (1975) Relationship between activity and sturcture in derivatives of clonidine. Ibid 25: 786–793

McLennan, P. L., Bentley, G. A. (1978) Studies on the cadiovascular depressor actions of St 91—an analogue of clonidine. Eur. J. Pharmacol. 52: 251–257

McLennan, P. L., Bentley, G. A. (1983) Effects of prazosin and piperoxan on central cardiovascular actions of St 91 in cats. Ibid 86:19–26

Nayler, W. G., Price, J. M., Swann, J. B., McInnes, I., Race, D., Lower, T. E. (1968) Effect of the hypotensive drug St 155 (catapres) on the heart and peripheral circulation., J. Pharmacol Exp. Ther. 164: 45–59

Pichler, L., Kobinger, W. (1981) Centrally mediated cardiovascular effects of B-HT 920 (6-Allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]-azepine dihydrochloride), a hypotensive agent of the "clonidine type". J. Cardiovasc. Pharmacol. 3: 269–277

Quiroz, A. C., Eilen, S. D., Sander, G. E., Giles, T. D. (1983) The effect of intravenous clonidine hydrochloride on the isolated forearm venous segment in heart failure. Chest 83 (Suppl.): 430S-433S

Schmitt, H. (1977) The pharmacology of clonidine and related products. In: Cross, F. (ed) Handbook Exp. Pharmacol. Vol. 39, Springer-Verglag, Berlin, pp 299–397

Shepherd, J. T., Vanhoutte, P. M. (1975) Veins and their control. W. B. Saunders Company Ltd., London, pp. 1–20, 99–170