Br. J. clin. Pharmac. (1983), **16**, 451–455

AN ASSESSMENT OF THE CONTRIBUTION OF CLONIDINE METABOLISED FROM ALINIDINE TO THE CARDIOVASCULAR EFFECTS OF ALINIDINE

D.W.G. HARRON, D. ARNDTS[1], M. FINCH & R.G. SHANKS

Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Northern Ireland, and [1]Boehringer Ingelheim KG, West Germany

Five healthy volunteers (mean age 20.6 years, mean weight 71 kg) received in random order on day 1 and day 8 a single dose of alinidine 40 mg, clonidine 0.1 mg or placebo and on days 2–7 alinidine 40 mg, clonidine 0.1 mg or placebo given three times a day with 1 week between treatment periods. Blood samples were taken for measurement of concentrations of alinidine and clonidine during alinidine administration and of clonidine during clonidine dosing. Heart rate and blood pressure were recorded in supine and standing positions and heart rate after 3 min exercise. Plasma concentrations of alinidine reached a maximum of 163.6 ± 10.0 ng/ml 2 h after alinidine administration on day 1 and during chronic administration similar concentrations were achieved. Clonidine plasma concentrations reached 0.3 ± 0.11 ng/ml 6 h after alinidine 40 mg on day 1, and during chronic administration of alinidine, increased to a steady state on day 5 with trough and 2 h values of 0.73 ± 0.15 and 0.86 ± 0.14 ng/ml respectively. After the first dose of clonidine on day 1, the maximum plasma concentration of clonidine was 0.32 ± 0.1 ng/ml at 4 h, during chronic administration clonidine plasma concentration rose to 1.04 ± 0.14 ng/ml 2 h after a dose on day 5. Alinidine produced a greater reduction in the exercise tachycardia than clonidine. There was little difference in the effects of the two treatments on heart rate and blood pressure with subjects in the supine and standing positions. These observations confirm that clonidine is formed during the oral administration of alinidine but it is unlikely that this clonidine contributes to the reduction in the exercise tachycardia produced by alinidine.

Keywords alinidine clonidine cardiovascular effects

Introduction

Alinidine, the *N*-allyl derivative of clonidine, produces a sinus bradycardia which is unaffected by pretreatment with atropine or phentolamine in experimental animals (Kobinger *et al.*, 1979a, b). In man alinidine reduces supine and standing heart rate (Harron *et al.*, 1982a), and produces a dose dependent reduction in an exercise tachycardia with alinidine 80 mg having the same effect as propranolol 40 mg (Harron *et al.*, 1982a). Alinidine does not inhibit an isoprenaline tachycardia in animals (Kobinger *et al.*, 1979a) or in man (Harron *et al.*, 1982a). The metabolism of alinidine in man leads to the formation of small amounts of clonidine (Arndts & Forster, 1981; Harron *et al.*, 1982b). In five healthy volunteers, the oral administration of 40 mg alinidine twice daily for 7 days, produced plasma concentrations of clonidine in the range of 0.82 to 0.92 ng/ml 2 h after a dose of alinidine (Harron *et al.*, 1982b). Only a small amount of clonidine was formed from alinidine as the urinary excretion of clonidine represented 0.1% of the administered dose of alinidine.

Although it is unlikely that clonidine, metabolised from alinidine, contributes to the pharmacological effect of alinidine, it was felt essential to compare the effects on heart rate and blood pressure in man of the oral administration of alinidine and of clonidine, given in a dose to produce plasma levels of clonidine comparable to those expected from the administration of alinidine. Both drugs were administered for 7 days to ensure that steady state was obtained. Plasma concentrations of clonidine were measured during both treatments.

Methods

Observations were made in five healthy male subjects (mean age 20.6 years; mean weight 71 kg) who re-

ceived in random order for 1 week placebo, alinidine and clonidine on oral administration. On day 1 and day 8 the subjects received a single dose of alinidine 40 mg, clonidine 0.1 mg or placebo; on days 2–7 alinidine 40 mg, clonidine 0.1 mg or placebo were administered at 9.00, 15.00 and 21.00 h. The treatment periods were separated by 1 week. Blood samples were withdrawn from an antecubital vein on day 1 at 0, 2, 4, 6, 8 and 12 h, after the last dose on day 8 at 0, 2, 4, 6, 8, 12, 24, 32 and 48 h and on days 2–5 before and 2 h after administration of the 09.00 h dose. No samples were taken on days 6 and 7. The samples were centrifuged and plasma stored at −20°C until analysed. At each of these times (except 12 h on days 1 and 8) the subjects were supine for 15 min, stood for 3 min and then performed moderate/severe exercise by stepping on and off a box 46 cm high at a rate of 32 steps/min for 3 min. Heart rate and blood pressure were recorded (Critikon Exercise Monitor Model 1165) at the end of the periods in the supine and standing positions; heart rate was measured within 5 s of completing exercise. The study was approved by the University Ethical Committee.

The concentrations of alinidine in plasma samples were measured using a radioimmunoassay method (Arndts & Stähle, 1981) and the concentrations of clonidine measured by a specific radioimmunoassay (Arndts *et al.*, 1981). The intraassay coefficient of variation was less than 4% for clonidine and was 4% for alinidine while the interassay coefficient of variation ranged between 8.3% (clonidine) and 8.7% (alinidine). Plasma elimination half-lives of alinidine and clonidine were calculated by linear least squares regression analysis of the terminal part of the log concentration-time graph.

Results

The mean plasma concentrations of alinidine in the five subjects on days 1 to 5 and on day 8 are given in Table 1. The peak concentration on days 1 and 8 occurred 2 h after dose administration; there was little difference in the 2 h values on the 6 days on which measurements were made. The trough values (0 h) on days 3, 4, 5 and 8 were not different. These results indicate that no accumulation of alinidine occurred during the 7 days of drug administration. Clonidine was present in samples taken during the administration of alinidine. The plasma concentration of clonidine increased after administration of alinidine 40 mg on day 1 and reached a peak of 0.3 ± 0.11 ng/ml at 6 h (Table 1). The concentration of clonidine 2 h after dose administration increased progressively from

Table 1 Plasma concentrations of alinidine and clonidine during administration of alinidine and plasma concentrations of clonidine during administration of clonidine. Mean ± s.e. mean of observations in five subjects

Time		*Alinidine treatment*		*Clonidine treatment*
		Plasma alinidine (ng/ml)	*Plasma clonidine (ng/ml)*	*Plasma clonidine (ng/ml)*
Day 1	0	00.0 ± 0.0	0.00 ± 0.00	0.00 ± 0.00
	2	163.6 ± 10.0	0.13 ± 0.04	0.32 ± 0.10
	4	112.1 ± 8.6	0.20 ± 0.04	0.29 ± 0.05
	6	73.4 ± 4.6	0.30 ± 0.11	0.25 ± 0.04
	8	50.8 ± 3.8	0.25 ± 0.05	0.21 ± 0.04
	12	24.9 ± 2.5	0.20 ± 0.04	0.13 ± 0.04
Day 2	0	5.0 ± 0.8	0.09 ± 0.01	0.03 ± 0.01
	2	168.7 ± 6.3	0.23 ± 0.05	0.42 ± 0.04
Day 3	0	42.3 ± 2.8	0.42 ± 0.04	0.32 ± 0.07
	2	178.4 ± 8.8	0.63 ± 0.06	0.77 ± 0.07
Day 4	0	42.0 ± 3.0	0.65 ± 0.06	0.43 ± 0.07
	2	214.1 ± 23.0	0.84 ± 0.13	0.73 ± 0.13
Day 5	0	46.0 ± 6.7	0.73 ± 0.15	0.56 ± 0.09
	2	181.1 ± 17.5	0.86 ± 0.14	1.04 ± 0.14
Day 8	0	47.9 ± 9.1	0.57 ± 0.10	0.70 ± 0.17
	2	168.3 ± 23.2	1.07 ± 0.55	0.99 ± 0.17
	4	137.9 ± 13.0	0.70 ± 0.11	0.87 ± 0.13
	6	100.6 ± 9.6	0.69 ± 0.11	0.77 ± 0.14
	8	78.2 ± 7.5	0.68 ± 0.14	0.60 ± 0.11
	12	32.8 ± 2.3	0.48 ± 0.11	0.55 ± 0.16
	24	7.3 ± 0.5	0.18 ± 0.03	0.17 ± 0.06
	32	4.3 ± 1.3	0.13 ± 0.02	0.10 ± 0.04
	48	1.0 ± 0.7	0.03 ± 0.01	0.04 ± 0.02

0.13 ng/ml on day 1 to 0.86 ng/ml on day 5 and to 1.07 ng/ml on day 8. The trough (0 h) values increased from the third to fifth days when it was 0.73 ng/ml. Thus clonidine accumulated from day 1 with steady state being reached about day 5.

After administration of clonidine 0.1 mg on day 1, the maximum plasma concentration of clonidine occurred at 2 h. The concentration at 2 h increased from day 1 to day 5 and was the same on day 8 as day 5. The trough (0 h) concentrations increased from day 3 to day 8. Thus accumulation of clonidine occurred with steady state being reached about day 5.

The plasma elimination half-life of alinidine was 4.4 ± 0.2 h on day 1 and 6.0 ± 0.6 h after the last dose on day 8. The elimination half-life of clonidine during clonidine administration was 6.25 ± 1.0 h on day 1 and 8.26 ± 1.5 h on day 8.

Little change occurred in supine heart rate during administration of placebo. On days 3 and 4 supine heart rate was significantly less than placebo ($P < 0.05$) 2 h after the dose of alinidine (day 3; placebo 64.8 ± 4.0, alinidine 53.2 ± 1.7 beats/min: day 4; placebo 62.4 ± 4.4, alinidine 50.2 ± 2.7 beats/min). Similar effects were produced by clonidine (day 3, 53.0 ± 2.8; day 4, 50.2 ± 2.9 beats/min). At all other times supine heart rate was generally less during the administration of alinidine and clonidine but the differences from placebo were small and rarely significant. Standing heart rate was less during the administration of alinidine and clonidine but the differences from the placebo were small and only significant on some occasions.

The effects of placebo, alinidine and clonidine on exercise heart rate are given in Table 2. Clonidine produced small reductions in exercise heart rate which were significant ($P < 0.05$) 2 h after dose administration on days 3 and 4 and at 4 h on day 8. With the exception of the measurement at 0 h on day 2 exercise heart rate was always less during the administration of alinidine than during placebo treatment; on many occasions these differences were significant. The mean exercise heart rate 2 h after alinidine was between 16 and 23 beats/min less than the corresponding value after placebo administration. Alinidine consistently reduced exercise heart rate more than clonidine with the difference between the two drugs being more marked 2 h after dose administration.

The effects of placebo, alinidine and clonidine on systolic and diastolic pressure with the subjects in the supine position are given in Table 3. Both alinidine and clonidine reduced systolic and diastolic pressure to a small extent, with no consistent difference between them. The effects of the two drugs on blood pressure in the standing position was similar to that in the supine position.

Tiredness and lassitude were reported as adverse effects during the administration of both alinidine

Table 2 Mean (± s.e. mean) exercise heart rate in five subjects during oral administration of placebo, clonidine 100 μg and alinidine 40 mg on day 1 and day 8; and placebo, clonidine 100 μg and alinidine 40 mg three times a day on days 2–7

	Day 1					*Day 2*		*Day 3*		*Day 4*		*Day 5*		*Day 8*					
Time (h)	*0*	*2*	*4*	*6*	*8*	*0*	*2*	*0*	*2*	*0*	*2*	*0*	*2*	*0*	*2*	*4*	*6*	*8*	*24*	*32*	*48*
Placebo	160.4 ± 5.1	160.4 ± 4.1	158.4 ± 7.3	159.0 ± 3.7	163.0 ± 4.9	160.0 ± 2.8	157.8 ± 4.1	162.0 ± 3.1	160.4 ± 3.4	157.4 ± 3.1	157.0 ± 2.7	156.4 ± 5.3	155.0 ± 2.3	162.4 ± 4.1	154.6 ± 5.7	160.4 ± 2.6	158.8 ± 2.7	156.2 ± 1.5	158.2 ± 3.9	155.0 ± 3.7	157.0 ± 1.9
Clonidine	157.6 ± 5.8	152.6 ± 5.5	155.6 ± 5.6	152.8 ± 4.8	156.0 ± 5.8	151.2 ± 3.8	155.2 ± 5.4	153.4 ± 5.7	146.4* ± 5.5	150.8 ± 3.8	144.4 ± 5.2	154.8 ± 4.8	148.2* ± 5.3	157.0 ± 6.6	147.6 ± 4.5	149.4* ± 4.1	150.2 ± 5.1	151.2 ± 6.3	157.0 ± 5.6	159.2 ± 5.9	162.6 ± 6.5
Alinidine	164.2 ± 4.5	148.8** ± 5.8	150.2 ± 6.4	151.2 ± 4.0	152.0** ± 5.0	162.0 ± 4.8	141.8** ± 5.4	147.8 ± 5.6	140.4** ± 4.4	144.2 ± 4.7	134.8** ± 5.2	150.0 ± 9.3	139.8** ± 3.6	157.0 ± 6.9	137.6** ± 5.4	144.2** ± 4.7	145.6** ± 4.6	144.4** ± 4.6	159.8 ± 5.1	163.2 ± 5.0	165.2 ± 6.4

*$P < 0.05$ reductions when compared with placebo. **$P < 0.01$ reductions when compared with placebo

Table 3 Mean (± s.e. mean) systolic and diastolic blood pressure in five subjects in the supine position after the oral administration of placebo, clonidine and alinidine as described in the text

	Systolic blood pressure (mm Hg)																				
	Day 1					*Day 2*		*Day 3*		*Day 4*		*Day 5*		*Day 8*							
Time (h)	*0*	*2*	*4*	*6*	*8*	*0*	*2*	*0*	*2*	*0*	*2*	*0*	*2*	*0*	*2*	*4*	*6*	*8*	*24*	*32*	*48*
Placebo	116.8 ± 4.1	108.6 ± 3.9	108.0 ± 3.6	112.0 ± 2.6	112.4 ± 2.0	113.8 ± 1.6	109.2 ± 3.1	118.0 ± 2.9	115.2 ± 4.4	118.0 ± 2.5	110.8 ± 3.3	116.0 ± 6.4	119.0 ± 3.8	116.8 ± 5.1	113.6 ± 1.7	106.8 ± 2.0	110.8 ± 2.8	118.4 ± 3.2	114.0 ± 3.2	114.8 ± 3.7	112.8 ± 2.9
Clonidine	115.2 ± 3.3	105.4 ± 3.6	106.6 ± 3.7	104.2 ± 3.2	110.6 ± 4.6	114.4 ± 3.8	104.2 ± 3.7	108.8* ± 4.6	106.4 ± 1.7	115.2 ± 3.0	98.8* ± 7.3	115.8 ± 0.9	107.0* ± 4.7	118.4 ± 3.8	112.2 ± 5.3	108.4 ± 5.9	107.2 ± 2.9	111.0 ± 2.6	114.4 ± 3.7	117.0 ± 2.3	120.8 ± 3.8
Alinidine	117.4 ± 5.5	105.0 ± 5.3	101.8 ± 4.2	104.2 ± 3.2	108.6 ± 4.2	110.8 ± 5.0	102.0 ± 3.4	111.6 ± 3.9	104.0* ± 1.5	103.2* ± 7.2	101.2* ± 2.1	127.8 (**) ± 2.6	113.4 ± 3.0	116.4 ± 3.9	105.8 ± 4.1	106.2 ± 4.8	103.0 ± 4.5	101.2** ± 6.1	118.6 ± 4.8	126.2 (**) ± 3.4	118.6 ± 6.6
	Diastolic blood pressure (mm Hg)																				
Placebo	57.6 ± 6.2	55.8 ± 6.2	47.8 ± 7.4	56.6 ± 4.8	59.0 ± 4.4	47.0 ± 6.2	59.0 ± 7.4	55.0 ± 6.8	64.8 ± 8.0	49.2 ± 9.7	58.6 ± 5.2	49.6 ± 8.1	48.6 ± 4.2	56.0 ± 6.0	57.8 ± 9.0	60.4 ± 8.6	55.0 ± 7.9	57.8 ± 4.5	55.6 ± 7.9	58.8 ± 7.3	64.6 ± 11.1
Clonidine	57.0 ± 5.4	52.4 ± 7.3	51.8 ± 5.9	58.2 ± 7.8	55.8 ± 6.0	57.8 (*) ± 9.3	43.6** ± 4.0	56.6 ± 4.8	53.6* ± 5.5	52.6 ± 6.0	46.0** ± 2.9	50.6 ± 6.9	47.8 ± 6.6	43.0** ± 3.5	54.4 ± 3.9	46.0** ± 4.1	46.8 ± 5.5	54.2 ± 4.4	53.0 ± 5.6	44.0** ± 4.9	48.6** ± 5.5
Alinidine	62.2 ± 5.5	59.0 ± 3.1	56.4 ± 2.6	58.6 ± 3.1	56.4 ± 7.0	55.0 ± 6.9	56.6 ± 3.2	53.0 ± 6.4	61.0 ± 1.7	52.6 ± 6.5	49.8 ± 4.7	47.2 ± 7.6	48.8 ± 7.3	44.0* ± 3.6	50.8 ± 8.0	44.4** ± 4.5	50.4 ± 5.2	48.6* ± 6.5	56.0 ± 3.9	51.0 ± 4.7	56.6* ± 4.5

* $P < 0.05$ reduction when compared to placebo, ** $P < 0.01$ reduction when compared to placebo
(*) $P < 0.05$ increase when compared to placebo

and clonidine; these effects were more marked on days 1 and 2 and tended to disappear after the third day.

Discussion

The results of the present study confirm earlier observations (Harron *et al.*, 1982b) which showed that after the oral administration of alinidine to man, clonidine was present in the plasma. It was concluded that in the metabolism of alinidine clonidine was formed with about 0.1% of the dose of alinidine appearing in the urine as clonidine. In the present study, in which alinidine was given for 8 days to healthy subjects, clonidine was present in the blood sample 2 h after the first dose and reached a peak at 6 h. The plasma concentrations of clonidine before and 2 h after a dose of alinidine increased until the fifth day. These concentrations of clonidine were similar to those occurring during the oral administration of clonidine 100 μg three times daily which is the usual therapeutic dose of clonidine (Dollery *et al.*, 1976; Davis *et al.*, 1977. Only small amounts of clonidine were formed from alinidine with the trough concentration of clonidine being about 2% of the concentration of alinidine, and the peak concentration of clonidine (on day 8) being less than 1% of the concentration of alinidine.

In the present study alinidine produced small reductions in heart rate in subjects in the supine and standing positions, with greater and significant reductions occurring in an exercise tachycardia. There was little difference in the effects of alinidine and clonidine on supine and standing heart rate. Although clonidine reduced an exercise heart rate, its effect was less than that of alinidine. In a previous study we found that clonidine had no effect on an exercise tachycardia (Harron *et al.*, 1982b). There is no apparent reason for the difference in the effects of clonidine in the two studies although the number of subjects in each was small. These results support the concept that the effect of alinidine in reducing heart rate and in particular exercise heart rate is not due to the action of clonidine formed from alinidine.

As both drugs produced small equivalent reductions in arterial pressure in the supine and standing positions, it is not clear if these effects during the administration of alinidine were due to clonidine or to a specific effect of alinidine. As the side effects of drowsiness and lethargy were similar with both drugs, it is probable that these were due to clonidine in both cases. Previous studies have shown that these side effects occur about 8–10 h after a single dose of alinidine, when the plasma level of alinidine has fallen to a much greater extent than that of clonidine.

It would appear that the oral administration for 8 days of doses of alinidine to produce its pharmacological effect leads to the formation of clonidine with plasma concentrations being similar to those occurring with the administration of therapeutic doses of clonidine but that this clonidine is not responsible for the bradycardia action of alinidine.

We would like to thank Dr K. Jady, Boehringer Ingelheim Ltd, for the supply of alinidine and for financial support.

References

ARNDTS, D. & FORSTER, H.J. (1981). New aspects in the metabolism of alinidine in man. *Eur. J. Drug Metab. Pharmacokin.*, **6**, 313–315.

ARNDTS, D. & STÄHLE, H. (1981). Development and quality control of a highly sensitive radioimmunoassay for alinidine. *J. pharmac. Methods*, **6**, 109–120.

ARNDTS, D., STÄHLE, H. & FORSTER, H.J. (1981). Development of a RIA for clonidine and its comparison with alternative reference methods. *J. pharmac. Methods*, **6**, 295–307.

DOLLERY, C.T., DAVIES, D.S., DRAFFAN, H.J., DARGIE, H.J., DEAN, C.R., REID, J.H., CLARKE, R.A. & MURRAY, S. (1976). Clinical pharmacology and pharmacokinetics of clonidine. *Clin. Pharmac. Ther.*, **19**, 11–17.

DAVIES, D.S., WING, L.M.H., REID, J.L., NEILL, E., TIPPET, P. & DOLLERY, C.T. (1977). Pharmacokinetics and concentration-effect relationships of intravenous and oral clonidine. *Clin. Pharmac. Ther.*, **21**, 593–601.

HARRON, D.W.G., JADY, K., RIDDELL, J.G. & SHANKS, R.G. (1982a). Effects of alinidine, a novel bradycardia agent on heart rate and blood pressure in man. *J. cardiovascular Pharmac.*, **4**, 213–220.

HARRON, D.W.G., ARNDTS, D. & SHANKS, R.G. (1982b). Alinidine pharmacokinetics following acute and chronic dosing. *Br. J. clin. Pharmac.*, **13**, 821–827.

KOBINGER, W., LILLIE, C. & PICHLER, L. (1979a). N-allyl-derivative of clonidine, a substance with specific bradycardia action at a cardiac site. *Naunyn-Schmeideberg's Arch. Pharmac.*, **306**, 255–262.

KOBINGER, W., LILLIE, C. & PICHLER, L. (1979b). Cardiovascular actions of N-allyl clonidine (ST567), a substance with specific bradycardia action. *Eur. J. Pharmac.*, **58**, 141–150.

REID, J.L., WING, L.M.H., MATHIAS, C.J., FRANKEL, H.L. & NEILL, E. (1977). The central hypotensive effect of clonidine studies in tetraplegic subjects. *Clin. Pharmac. Ther.*, **21**, 375–381.

(Received January 17, 1983, accepted June 20, 1983)