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Alinidine biotransformation in healthy Sudanese Arabs

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Summary

The biotransformation of alinidine (N-allyl clonidine) to clonidine was studied in 5 healthy Sudanese Arabs following acute and chronic administration of alinidine, 40 mg orally for 8 days. The results indicate that a small amount of clonidine is formed; this reached a maximum of 1.0 ± 0.47 ng/ml on day 4 following administration of alinidine, 40 mg 3 times a day. The concentration of clonidine formed from alinidine was not significantly different from that seen in a Caucasian study on healthy volunteers (0.92 ± 0.28 ng/ml) following administration of alinidine, 40 mg twice daily. The side-effects reported most frequently included tiredness, lethargy and dry mouth.

Introduction

Alinidine (ST567), the N-allyl derivative of clonidine reduces heart rate both in experimental animals and in man. The bradycardia does not result from blockade of cardiac beta-adrenoreceptors or from effects on alpha-adrenoreceptors or muscarinic receptors (Kobinger et al., 1979a and b; Harron et al., 1981). Recent pharmacokinetics studies in healthy Caucasian subjects have indicated that following acute administration of alinidine, 40 mg, 0.1% of the dose of alinidine was metabolized to clonidine; following chronic administration of alinidine, 40 mg twice daily, plasma levels of clonidine were 0.8–1.0 ng/ml (Harron et al., 1982). The purpose of this

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investigation was to evaluate the effect of race on the metabolism of alinidine to clonidine following acute and chronic administration of alinidine.

Materials and methods

The subjects were 5 healthy, male, Sudanese students (age 23.8 ± 0.4 years, weight 55.2 ± 2.6 kg (mean ± S.E.M.)); they were from different areas or tribes in the Sudan (Costi, Dongaláwi, Ga'aliin, Sháikia and Halawiin) although all tended to be from the centre and north of the country, which has a strong Arab influence. The subjects were administered on day 1, alinidine, 40 mg, at 08.00 h; on days 2–7 alinidine, 40 mg, was given 3 times a day at 08.00, 15.00 and 22.00 h and on day 8, alinidine, 40 mg, was administered at 08.00 h. Blood samples were taken for alinidine and clonidine determination on day 1, prior to drug administration and 2, 4, 6 and 24 h after administration. On days 2–5, blood samples were taken prior to and 2 h after drug administration and on day 8 blood samples were taken prior to and 2, 4, 6, 24,

TABLE I

PLASMA CONCENTRATIONS OF ALINIDINE (ng/ml)

Time (h)	Subject K.K.	Subject O.H.	Subject M.I.	Subject O.E.	Subject F.E.	Mean ± S.D.M.
0.00	0.000	0.000	0.000	–	–	–
2.00	232.650	178.440	210.980	152.361	173.72	189.6 ± 31.9
4.00	106.050	100.760	122.540	92.20	111.68	106.6 ± 11.4
6.00	59.450	81.960	93.140	61.52	101.72	79.6 ± 18.8
24.00	0.000	0.000	0.000	7.86	13.95	4.4 ± 6.3
26.00	196.450	154.200	333.220	219.36	166.48	213.9 ± 71.4
48.00	39.950	80.240	65.660	54.85	80.32	64.2 ± 17.3
50.00	221.950	291.560	277.460	189.28	–	245.1 ± 47.8
72.00	59.660	95.800	117.270	87.71	80.37	88.2 ± 21.1
74.00	294.650	338.240	313.740	256.00	263.28	293.2 ± 34.4
96.00	52.410	67.290	78.760	79.81	76.05	70.9 ± 11.4
98.00	246.350	311.560	389.900	273.12	296.68	303.5 ± 54.2
168.00	–	79.710	77.618	34.46	108.54	75.1 ± 30.5
170.00	229.450	393.480	325.020	166.60	–	278.7 ± 100.5
172.00	125.550	235.960	281.620	118.24	219.68	196.2 ± 71.6
174.00	73.850	153.360	300.580	78.56	219.84	165.2 ± 96.6
192.00	0.000	1.590	0.000	10.15	23.62	7.1 ± 10.2
198.00	0.000	0.000	0.000	7.36	12.43	4.0 ± 5.7
216.00	0.000	0.000	0.000	0.000	5.03	1.0 ± 2.21

Mean plasma concentrations ng/ml (±S.D.) of alinidine in 5 healthy Sudanese subjects following administration on day 1 of alinidine, 40 mg; on days 2–7, alinidine, 40 mg, three times a day and on day 8 alinidine, 40 mg, once. Plasma samples for alinidine determination were taken on day 1 prior to administration and at 2, 4, 6 and 24 h after administration; on days 2–5 prior to and 2 h after administration of the morning dose and on day 8, prior to and 2, 4, 6, 24, 30 and 48 h after the dose.

30 and 48 h after administration. The samples were centrifuged, the plasma separated and stored at −20°C until assayed.

The drug formulation of alinidine (Boehringer Ingelheim) was 40 mg tablets, lot. no. 00232. The concentration of alinidine in the plasma samples was determined using a radio-immunoassay method (Arndts and Stahle, 1981). Clonidine was measured using a clonidine-specific radio-immunoassay (Arndts et al., 1981).

Results

The plasma levels (Table 1) on day 1 following oral administration of 40 mg alinidine, decreased from a maximum of 189.6 ± 31.9 ng/ml (mean ± S.D., n = 5) at 2 h to 4.4 ± 6.3 ng/ml at 24 h.The plasma levels on days 2, 3, 4 and 5, two hours after administration of the morning dose were 213.9 ± 71.4, 245.1 ± 47.8, 293.2 ± 34.4 and 303.5 ± 54.2 ng/ml, respectively; the trough values of alinidine prior to administration of each morning dose were 64.2 ± 17.3, 88.2 ± 21.1, 70.9 ± 11.4 and 75.1 ± 30.5

TABLE 2

PLASMA CONCENTRATIONS OF CLONIDINE (ng/ml)

Time (h)	Subject K.K.	Subject O.H.	Subject M.I.	Subject O.E.	Subject F.E.	Mean ± S.D.M.
0.00	0.000	0.000	0.000	0.00	0.00	0.0
2.00	0.120	0.230	0.090	0.43	0.29	0.23 ± 0.14
4.00	0.280	0.440	0.190	0.52	0.39	0.36 ± 0.13
6.00	0.240	0.490	0.170	0.40	0.38	0.34 ± 0.13
24.00	0.100	0.100	0.140	0.32	0.30	0.19 ± 0.11
26.00	0.320	0.230	0.260	0.75	0.44	0.40 ± 0.21
48.00	0.390	0.410	0.400	0.50	0.58	0.46 ± 0.08
50.00	0.620	0.520	0.800	0.62	–	0.64 ± 0.12
72.00	0.480	0.690	1.440	0.57	0.61	0.76 ± 0.39
74.00	0.660	0.630	1.770	0.73	0.79	0.92 ± 0.48
96.00	0.540	0.770	1.810	0.55	0.54	0.84 ± 0.55
98.00	0.680	1.040	1.820	0.70	0.81	1.00 ± 0.47
68.00	–	0.590	1.240	0.46	0.56	0.71 ± 0.36
70.00	0.170	0.900	1.120	0.51	–	0.68 ± 0.42
172.00	0.210	1.060	0.990	0.51	0.73	0.70 ± 0.35
174.00	0.240	0.990	1.040	0.48	0.72	0.69 ± 0.34
192.00	0.120	0.290	0.490	0.33	0.40	0.33 ± 0.14
198.00	0.120	0.260	0.460	0.33	0.40	0.31 ± 0.13
216.00	0.040	0.070	0.210	0.00	0.28	0.12 ± 0.12

Mean plasma concentration (± S.D.) of clonidine (ng/ml) in 5 healthy Sudanese subjects following administration on day 1 of alinidine, 40 mg; on days 2–7, alinidine, 40 mg, three times a day and on day 8 alinidine, 40 mg, once. Plasma samples for drug determination were taken on day 1 prior to administration and at 2, 4, 6 and 24 h after administration; on days 2–5 prior to and 2 h after administration of the morning dose and on day 8, prior to and 2, 4, 6, 24, 30 and 48 h after the dose.

TABLE 3

Study	Sample time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8
(a) Alinidine (ng/ml)							
Acute (Caucasian)	0 h	–	5.3 ± 1.6				
40 mg alinidine	2 h	166.5 ± 18.5	–				
(n=5)							
Chronic (Caucasian)	0 h	–	9.03 ± 6.7	9.56 ± 7.5	11.94 ± 7.8	20.7 ± 26.0	10.6 ± 5.9
40 mg alinidine	2 h	202.9 ± 107.5	223.1 ± 123.9	211.61 ± 118.7	230.1 ± 119.3	217.5 ± 116.4	232.6 ± 61.8
daily×8 days							
(n=5)							
Chronic (Caucasian)	0 h	–	80.0 ± 35.8	110.8 ± 76.1	113.9 ± 58.7	106.1 ± 133.5	98.6 ± 34.6
40 mg alinidine	2 h	229.4 ± 65.1	356.2 ± 102.2	356.7 ± 100.1	331.7 ± 127.3	348.7 ± 158.9	336.3 ± 92.0
twice daily×8 days							
(n=4)							
Acute (Sudanese) day 1	0 h	–	4.4 ± 6.3	64.2 ± 17.3	88.2 ± 21.1	70.9 ± 11.4	75.1 ± 30.5
followed by chronic	2 h	189.6 ± 31.9	213.9 ± 71.4	245.1 ± 47.8	293.2 ± 34.4	303.5 ± 54.2	278.7 ± 100.5
40 mg							
alinidine thrice							
daily on days 2–8							
(n=5)							

(b) Clonidine (ng/ml)										
Acute (Caucasian)	0 h	–	0.12 ±	0.07						
40 mg alinidine	(8.4 ± 2.2 h)	0.26 ± 0.06	–							
(n = 5)										
Chronic (Caucasian)	0 h	–	0.19 ±	0.06	0.15 ±	0.09	0.25 ±	0.11	0.36 ±	0.31
40 mg alinidine	2 h	0.43 ± 0.28	0.47 ±	0.18	0.45 ±	0.19	0.54 ±	0.18	0.40 ±	0.22
daily × 8 days		(8 h)								
(n = 5)										
Chronic (Caucasian)	0 h	–	0.56 ±	0.32	0.71 ±	0.22	0.72 ±	0.18	0.47 ±	0.24
40 mg alinidine	2 h	0.56 ± 0.32	0.84 ±	0.21	0.92 ±	0.28	0.91 ±	0.05	0.88 ±	0.64
twice daily × 8 days		(24 h)								
(n = 4)										
Acute (Sudanese)	0 h	–	0.19 ±	0.11	0.46 ±	0.08	0.76 ±	0.39	0.84 ±	0.55
day 1	2 h	0.36 ± 0.13	0.40 ±	0.21	0.64 ±	0.12	0.92 ±	0.48	1.00 ±	0.47
followed by chronic		(4 h)								
40 mg										
alinidine thrice										
daily on days 2–8										
(n = 5)										

0.23 ±	0.11									
0.64 ±	0.12									
(4 h)										
0.71 ±	0.19									
0.86 ±	0.42									
0.68 ±	0.42									
0.70 ±	0.35									
(1 h)										

(a) Mean peak and trough plasma levels (± S.D.) of alinidine in previous acute and chronic alinidine studies (Harron et al., 1982) in healthy Caucasian subjects and comparison with the acute and chronic administration of alinidine to 5 healthy Sudanese subjects. (b) Mean peak and trough plasma level (± S.D.) of clonidine in previous acute and chronic alinidine studies (Harron et al., 1982) in healthy Caucasian subjects and comparison with the acute and chronic administration of alinidine to 5 healthy Sudanese subjects. Times in parentheses indicate time of peak clonidine concentration.

ng/ml on days 3, 4, 5 and 8, respectively. No accumulation of alinidine occurred during the study. Following administration of alinidine, 40 mg, on day 8, the maximum plasma level was seen 2 h after administration (278.7 ± 100.5 ng/ml) and decreased until at 48 h after the final dose the concentration was 1.0 ± 2.2 ng/ml.

Clonidine was detected in the plasma samples following administration of alinidine, 40 mg, on day 1. The clonidine plasma concentration (Table 2) rose from 0.23 ± 0.14 ng/ml at 2 h to 0.36 ± 0.13 ng/ml at 4 h after administration and fell back to 0.19 ± 0.11 ng/ml at 24 h. The clonidine concentrations 2 h after the morning dose were 0.4 ± 0.21, 0.64 ± 0.12, 0.92 ± 0.48, 1.0 ± 0.47 and 0.68 ± 0.42 ng/ml on days 2, 3, 4, 5 and 8, respectively; the trough concentrations of clonidine were 0.46 ± 0.08, 0.76 ± 0.39, 0.84 ± 0.55 and 0.71 ± 0.36 on days 3, 4, 5 and 8, respectively. Accumulation of clonidine did not occur after day 4 of the study. On day 8 clonidine levels reached a maximum at 4 h (0.7 ± 0.35 ng/ml). The maximum clonidine plasma level achieved by any subject was (with subject M.I.) 1.82 ng/ml 2 h after the morning dose on day 4 (day 3 of the chronic study). The areas under the curves (AUC) (trapezoidal rule) for alinidine were 28,460, 25,640, 29,860, 23,787 and 27,983 ng ml^{-1} h and for clonidine 69, 140, 219, 80 and 118 ng ml^{-1} h for subjects K.K., O.H., M.I., O.E., and F.F., respectively.

Discussion

Comparison of the plasma levels of alinidine in previous studies (Harron et al., 1982) with the current study (Table 3a) show similar plasma levels on day 1; however, with chronic administration the plasma levels prior to drug administration and 2 h after administration of the morning dose of alinidine, 40 mg, three times a day in the Sudanese subjects are lower than those in the Caucasian subjects taking alinidine, 40 mg, twice daily.

Previous studies have shown that following acute administration of alinidine, 40 mg, 0.1% of the alinidine dose is converted to clonidine (Arndts and Forster, 1981; Harron et al., 1982). Following chronic dosing of alinidine, 40 mg, daily for 8 days in healthy Caucasian subjects (Harron et al., 1982) the plasma levels of clonidine (Table 3b) reached 0.54 ± 0.18 ng/ml on day 4; following alinidine, 40 mg, twice daily in the same subjects, the plasma levels of clonidine reached 0.92 ± 0.28 ng/ml on day 3. This level of clonidine after alinidine, 40 mg, twice daily is in the range occurring after oral administration of the therapeutic dose (300 μg) of clonidine (Davies et al., 1977). The maximum clonidine levels in the current Sudanese study on day 1 (0.36 ± 0.13 at 4 h) were similar to those seen in the previous studies (Table 3b). However, on day 3 in the Sudanese study (day 4 of the chronic study, 40 mg three times daily) the mean clonidine plasma level was 1.0 ± 0.47 ng/ml compared with the level on day 4 of the Caucasian study (40 mg twice daily) of 0.92 ± 0.28 ng/ml. In all studies alinidine and clonidine had virtually disappeared from the plasma 48 h after the last dose.

The side-effects reported most frequently included tiredness, lethargy, dry mouth; there were isolated reports of nausea, diarrhoea, constipation, abnormal heart beats, headache and loss of appetite.

This study indicates that a small amount of clonidine is formed from alinidine in healthy Sudanese Arabs and the extent of metabolism appears to be similar to that seen in healthy Caucasian subjects.

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References

Arndts, D. and Stahle, H., Development and quality control of a highly sensitive radioimmunoassay for alinidine. J. Pharmacol. Meth., 6 (1981) 109–120.

Arndts, D. and Forster, H.J., New aspects in the metabolism of alinidine in man. Eur. J. Drug Metab. Pharmacokin., 6 (1981) 313–315.

Arndts, D., Stahle, H. and Forster, H.J., Development of a RIA for clonidine and its comparison with alternative reference methods. J. Pharmacol. Meth., (1982) in press.

Davies, D.S., Wing, L.M.H., Reid, J.L., Neill, E., Tippet, P. and Dollery, C.T., Pharmacokinetics and concentration–effect relationships of intravenous and oral clonidine. Clin. Pharmacol. Ther., 21 (1977) 593–601.

Harron, D.W.G., Arndts, D. and Shanks, R.G., Alinidine pharmacokinetics following acute and chronic dosing. Br. J. Clin. Pharmacol., 13 (1982) 821–827.

Harron, D.W.G., Riddell, J.G. and Shanks, R.G., Alinidine reduces heart rate without blockade of beta-adrenoceptors. Lancet, i. (1981) 351–353.

Kobinger, W., Lillie, C. and Pichler, L. N-allyl-derivative of clonidine, a substance with specific bradycardiac action at a cardiac site. Naunyn-Schmiedeberg's Arch. Pharmacol., 306 (1979a) 255–262.

Kobinger, W., Lillie, C. and Pichler, L., Cardiovascular actions of N-allyl clonidine (St567), a substance with specific bradycardiac action. Eur. J. Pharmacol., 58 (1979b) 141–150.