ALINIDINE PHARMACOKINETICS FOLLOWING ACUTE AND CHRONIC DOSING

D.W.G. HARRON, D. ARNDTS¹ & R.G. SHANKS

Department of Therapeutics and Pharmacology, The Queen's University, Belfast, Northern Ireland and ¹Boehringer Ingelheim KG., Ingelheim Am Rhein, W. Germany

1 Alinidine (*N*-allyl clonidine) pharmacokinetics were investigated in healthy volunteers following acute administration of 40 mg orally and intravenously (i.v.) and chronic administration of 40 mg daily and twice daily for 8 days.

2 After acute oral administration the following values were obtained; $C_{\max}$ – 166.5 ± 18.5 ng/ml at 1.8 ± 0.7 h (mean $\pm$ s.d., $n = 5$); AUC – 1122.9 ng ml⁻¹ h; Vd_{ss} – 190.7 l and $T_{1/2}$ – 4.2 h, and after i.v. administration: AUC – 1046.7 ng ml⁻¹ h; Vd_{ss} – 190.7 l and $T_{1/2}$ 4.2 h.

3 Clonidine was identified in plasma and urine samples following oral and i.v. administration; clonidine $C_{\max}$ was 0.26 ± 0.06 ng/ml at 8.4 ± 2.2 h and 0.5 ± 0.2 ng/ml at 4.8 ± 2.5 following oral and i.v. alinidine respectively. Urinary excretion of clonidine represented 0.1% of the administered dose of alinidine.

4 During administration of alinidine 40 mg daily for 8 days, peak and trough plasma levels reached steady state after day 2 (223.1 ± 123.9 and 9.03 ± 6.7 ng/ml respectively). During alinidine 40 mg twice daily for 8 days peak and trough plasma levels on day 2 were 356.2 ± 92.0 and 80.0 ± 35.8 ng/ml respectively, these levels did not change ($P > 0.05$) between days 2 and 8. Urine elimination of alinidine did not change ($P > 0.05$) between days 5, 6, 7 and 8.

5 Clonidine plasma concentration following alinidine 40 mg daily and twice daily were 0.47 ± 0.18 and 0.84 ± 0.21 ng/ml respectively 2 h after administration on day 2 and did not change ($P < 0.05$) between days 2–8.

6 It is unlikely that clonidine formed from alinidine contributes to the pharmacological action of alinidine.

Introduction

Alinidine (ST567), the *N*-allyl-derivative of clonidine, has novel pharmacological properties in animals and in man. Alinidine reduced the rate of spontaneously beating isolated atria and heart rate in anaesthetised animals (Kobinger *et al.*, 1979 a,b). Alinidine reduced heart rate in normal subjects in the supine and standing positions with a more marked reduction in an exercise tachycardia; the latter effect was comparable to that produced by propranolol (Harron *et al.*, 1981). The mechanism of this bradycardic action has not been elucidated as it did not result from blockade of cardiac β -adrenoceptors or from effects on α -adrenoceptors or muscarinic receptors (Harron *et al.*, 1981; Kobinger *et al.*, 1979 a,b.).

As alinidine is closely related to clonidine, it is necessary to ascertain if alinidine is metabolised to clonidine which might then contribute to the pharma-

cological effects of the parent drug in intact animals and man. Sensitive specific radioimmunoassays have now been established for the measurement of alinidine and clonidine in the presence of each other (Arndts & Stähle, 1982; Arndts *et al.*, 1981a). These assays have been used to measure the plasma concentrations in normal subjects of alinidine and clonidine after oral and intravenous administration of a single dose of alinidine and after oral administration of alinidine 40 mg daily and twice daily for 8 days.

Methods

In the first study alinidine 40 mg was administered in random order orally and intravenously to five healthy male volunteers (mean age 23 years, mean weight 70 kg) following an overnight fast, with 1 week between

treatments. Following oral administration, blood samples for determination of drug content were obtained from an antecubital vein using an indwelling catheter before and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180 min, 3.5, 4, 5, 6, 8, 12 and 24 h. For intravenous administration, alinidine was infused over 10 min into a vein in the left arm and blood samples withdrawn, using an indwelling venous catheter, from the right arm, on completion of the infusion and at 2, 5, 10, 20, 30, 40, 50, 60, 75, 90, 120 min, 2.5, 3, 4, 5, 6, 8, 12, and 24 h after infusion. The samples were centrifuged and the plasma stored at -20°C until analysed. Total urine collections were made following both oral and intravenous administration from 0–4, 4–8, 8–12, and 12–24 h; the urine volumes were measured, samples taken for drug determination and stored at -20°C until analysed.

In the second study alinidine was administered for 8 days either as 40 mg once daily or 40 mg twice daily (09.00 h and 21.00 h) to five healthy male volunteers (mean age 24 years, mean weight 70 kg), in random order with 1 week between treatments. Blood samples for drug determinations were taken by direct venepuncture on day 1 before drug administration (09.00 h) and at 1, 2, 4, 6, 8 and 12 h; on days 2, 3, 4 and 5 prior to drug administration and 2 h following this dose, and on day 8 before drug administration and at 1, 2, 4, 6, 8, 12, 24, 33 and 48 h. The samples were centrifuged and the plasma stored at -20°C until analysed. Urine samples (24 h) were taken for days 5, 6, 7 and 8, the volume measured and samples stored at -20°C until analysed.

The drug formulations of alinidine were (a) sterile ampoules (Batch No. 9112) containing 20 mg/2 ml of alinidine and (b) capsules (Batch No 88805) containing 40 mg alinidine. Both formulations contained less than 100 p.p.m. clonidine.

The concentrations of alinidine in plasma and urine samples were determined using a radioimmunoassay method (Arndts & Stahle, 1982). Clonidine in the plasma and urine samples was measured using a clonidine specific radioimmunoassay (Arndts *et al.*, 1981a). The intraassay coefficient of variation (CV) was less than 4% for clonidine and was 4% for alinidine while the interassay (CV) ranged between 8.3% (clonidine) and 8.7% (alinidine). The experimental results using unweighted data were mathematically described by an open three compartment model (Arndts *et al.*, 1981b). The differential equations of this model were integrated according to Wolf *et al.* (1977), and the analytical functions of the central compartment were individually fitted to the experimentally determined plasma concentrations. The fitting was performed by variation of the system parameters (α , β , γ and the compartmental transfer constants) using a search algorithm with an IBM 370–168 computer. This model was further used to

simulate plasma concentration curves after chronic alinidine administration. The curve fitting was optimized according to the maximum value of the approximation criterium K:

$$K = 1 - \frac{\sum (Y_i - f_i)^2}{\sum Y_i^2}$$

where Y_i denoted the experimental data at time i and f_i represents the corresponding function values calculated. The transfer constants were first evaluated by curve fitting the experimental data obtained from the intravenous trial. These values were kept constant for curve fitting the experimental data obtained after oral administration. Statistical analyses were carried out using Student's paired t -test.

Results

Acute study

Following intravenous administration of 40 mg alinidine, the plasma concentration of alinidine fell rapidly from 921.7 ± 353.6 ng/ml (mean $\pm$ s.d.) at the end of infusion to 162.2 ± 49.3 ng/ml after 1 h (Figure 1). After 40 mg alinidine orally plasma levels of alinidine rose from 4.7 ± 1.2 ng/ml 15 min after administration to 120.1 ± 46.1 ng/ml at 1 h; the maximum concentration ($C_{\max}$) was 166.5 ± 18.5 ng/ml at 1.8 ± 0.7 h ($t_{\max}$). Between 1 h and 24 h the log plasma concentration/time profiles for alinidine following intravenous and oral administration were similar (Figure 1).

Clonidine was also identified in the alinidine samples and the mean concentrations are given in Figure 1. The plasma levels of clonidine increased following intravenous administration from 0.03 ± 0.02 ng/ml at the end of infusion to 0.31 ± 0.17 ng/ml at 3 h; the maximum concentration ($C_{\max}$) was 0.5 ± 0.2 ng/ml at 4.8 ± 2.5 h and fell to 0.3 ± 0.2 ng/ml at 24 h. Following oral administration clonidine plasma levels increased from 0.02 ± 0.02 ng/ml 30 min after administration to 0.2 ± 0.08 ng/ml at 3 h; the maximum concentration ($C_{\max}$) was 0.26 ± 0.06 ng/ml at 8.4 ± 2.2 h and fell to 0.12 ± 0.07 ng/ml at 24 h. Clonidine in the alinidine samples had previously been identified by mass spectrometry (Arndts & Forster, 1982).

The computer model (Arndts *et al.*, 1981b) was applied to the experimentally determined plasma concentrations obtained in the present acute study, and the pharmacokinetic parameters following intravenous and oral alinidine 40 mg calculated (Table 1). These results indicate that the plasma elimination half life was 4.2 h (coefficient of variation (CV) 42.5%), following intravenous administration of alinidine. No significant differences ($P < 0.05$) occurred following

Figure 1 The mean ($\pm$ s.d., $n = 5$) plasma concentrations of alinidine (●) and clonidine (○) following single dose administrations of 40 mg alinidine given intravenously or orally to healthy subjects.

Table 1 Pharmacokinetic parameters (mean $\pm$ coefficient of variation (CV) $n = 5$) in healthy subjects following single intravenous and oral administration of 40 mg alinidine; α β and γ = distribution and elimination phase constants; τ = lag time; V_{dss} = volume of distribution at steady state; k_{el} = overall 1st order elimination constant; $k_{el\text{ ren}}$ = 1st order renal elimination constant; AUC = area under the plasma concentration time curve; Cl_{tot} = Total clearance; Cl_{ren} = renal clearance; $T_{1/2\alpha}$ β and γ = half lives of the distribution and elimination phases; K = approximation criterium.

Definition	Single i.v. injection		Single oral administration	
	Mean (n = 5)	CV %	Mean (n = 5)	CV %
K (Mean)	0.9990		0.9851	
Dose (mg)	40	0.0000	40	0.0000
α (1/h)	77.1	41.6	77.1	41.6
β (1/h)	4.7	43.96	4.7	43.96
γ (1/h)	0.19	33.3	0.19	33.3
τ	0.25 (s)	233.6	0.25 (h)	0.8
V_{dss} (l)	190.7	51.5	190.7	21.9
k_{el} (h ⁻¹)	5.6	44.5	5.6	44.5
$k_{el\text{ ren}}$	4.6	48.3	4.3	45.7
AUC (ng ml ⁻¹ h)	1122.9	14.2	1046.7	20.3
Cl_{tot} (ml/min)	602.4	12.6	656.8	18.7
Cl_{ren} (ml/min)	480.7	20.76	513.3	12.6
$T_{1/2\alpha}$ (s)	39.6	56.4	39.6	56.4
$T_{1/2\beta}$ (min)	10.7	50.9	10.7	50.9
$T_{1/2\gamma}$ (h)	4.2	42.5	4.2	42.5

Table 2 Mean ($\pm$ s.d., $n = 5$) urine elimination of alinidine and clonidine between 0–4, 4–8, 8–12 and 12–24 h following administration of 40 mg alinidine intravenously and orally to healthy subjects.

Time (h)	Intravenous		Oral	
	Alinidine (μ g)	Clonidine (μ g)	Alinidine (μ g)	Clonidine (μ g)
0–4	19,668.8 $\pm$ 7154.2	11.0 $\pm$ 8.8	15,052.2 $\pm$ 3708.1	6.34 $\pm$ 2.4
4–8	6,933.2 $\pm$ 1098.4	8.3 $\pm$ 3.2	8,035.0 $\pm$ 1030.0	8.1 $\pm$ 5.0
8–12	3,464.2 $\pm$ 1330.9	8.1 $\pm$ 3.7	4,163.8 $\pm$ 978.9	6.6 $\pm$ 5.3
12–24	2,441.2 $\pm$ 887.4	15.4 $\pm$ 4.6	4,173.4 $\pm$ 2729.6	18.2 $\pm$ 14.3
Total eliminated	32,507 $\pm$ 8552	42.8 $\pm$ 12.2	31,424 $\pm$ 7006	38.7 $\pm$ 21.3

intravenous and oral administration in the areas under the plasma curves, the total clearance and the volume of distribution.

Total urine output was collected from 0–4, 4–8, 8–12 and 12–24 h following 40 mg alinidine orally and intravenously. The results (Table 2) indicate that the elimination of alinidine at each collection time was not significantly different between intravenous and oral administration. The percentage of each dose eliminated over 24 h was 81.5 ± 21.1 following intravenous administration and 78.6 ± 17.5 following oral administration. The amount of clonidine eliminated

over the 24 h (Table 2) following intravenous administration was $42.8 \pm 12.2 \mu\text{g}/24 \text{ h}$ ($0.1 \pm 0.03\%$ of the dose of alinidine) and following oral administration $38.7 \pm 21.3 \mu\text{g}/24 \text{ h}$ ($0.09 \pm 0.05\%$ of the dose of alinidine).

Chronic study

The plasma concentrations of alinidine following administration of 40 mg daily and 40 mg twice daily to five healthy volunteers are given in Figure 2. The peak plasma concentration following 40 mg alinidine

Figure 2 The mean ($n = 5$) plasma concentrations of alinidine (closed symbols) and clonidine (open symbols) observed during chronic administration of 40 mg alinidine given orally once daily ($\bullet$)/long arrows or twice daily ($\blacksquare$)/short arrows in healthy subjects. The interruptions of the curves represent those periods when no plasma samples were drawn.

daily on day 1 was 202 ± 107.5 ng/ml (mean $\pm$ s.d., $n = 5$) at 2 h and fell to 9.03 ± 6.7 ng/ml 24 h after administration; on days 2, 3, 4, 5 and 8 the plasma concentrations 2 h after administration of the daily dose were 223.1 ± 123.9 , 211.61 ± 118.7 , 230.1 ± 119.3 , 217.5 ± 116.4 and 232.6 ± 61.8 ng/ml respectively; the trough plasma levels prior to administration of the daily dose on days 2, 3, 4, 5, 8 and 9 were 9.03 ± 6.7 , 9.56 ± 7.5 , 11.94 ± 7.8 , 20.71 ± 26.0 , 10.6 ± 5.9 and 10.4 ± 8.3 ng/ml respectively. These results indicate that no accumulation of the drug was occurring.

The peak plasma concentration following the first dose of 40 mg alinidine twice daily on day 1 was 262.9 ± 125.4 ng/ml at 1 h, on days 2, 3, 4, 5 and 8 the plasma level 2 h after the morning dose of alinidine 40 mg was 356.2 ± 102.2 , 356.7 ± 100.1 , 331.7 ± 127.3 , 348.7 ± 158.9 and 336.3 ± 92.0 ng/ml respectively (mean $\pm$ s.d., $n = 4$), the trough levels prior to the administration of the morning dose on days, 2, 3, 4, 5 and 8 were 80.0 ± 35.8 , 110.8 ± 76.1 , 113.9 ± 58.7 , 106.1 ± 133.5 and 98.6 ± 34.6 ng/ml respectively. These values indicate that no accumulation of the drug was occurring.

The fluctuations between peak and trough plasma levels were less marked following alinidine 40 mg twice daily than alinidine 40 mg daily. The plasma elimination half life of alinidine during the first 12 h of the chronic study was 4.5 ± 1.5 h (40 mg daily) and 3.4 ± 1.4 h (40 mg twice daily); this increased when calculated over 48 h following the last dose of alinidine (day 8) to 6.3 ± 0.9 h (40 mg daily) and 7.1 ± 1.1 h (40 mg twice daily).

The plasma concentrations of clonidine following alinidine 40 mg daily and twice daily are shown in Figure 2. The peak plasma level of clonidine following 40 mg alinidine daily on day 1 was 0.43 ± 0.28 ng/ml (mean $\pm$ s.d., $n = 5$) at 8 h. The clonidine plasma level did not change significantly ($P > 0.05$) between 4 and 12 h. On days 2, 3, 4 and 5 the plasma level of clonidine 2 h after administration of alinidine was 0.47 ± 0.18 , 0.45 ± 0.19 , 0.54 ± 0.18 and 0.4 ± 0.22 ng/ml; on day 8 the peak plasma level was 0.64 ± 0.12 ng/ml at 4 h and remained constant with no significant changes occurring between 4 and 12 h. The trough clonidine plasma levels on day 2, 3, 4, 5, 8 and 9 were 0.19 ± 0.06 , 0.15 ± 0.09 , 0.25 ± 0.11 , $0.36 \pm$

0.31 , 0.23 ± 0.11 and 0.28 ± 0.1 ng/ml respectively indicating no accumulation of clonidine over the course of the study. Following 40 mg alinidine twice daily the peak plasma level of clonidine on day 1 was 0.54 ± 0.35 ng/ml at 6 h; it did not change significantly between 2 and 24 h. The clonidine plasma levels (mean $\pm$ s.d., $n = 4$) 2 h after administration of alinidine 40 mg twice daily on days 2, 3, 4 and 5, were 0.84 ± 0.21 , 0.92 ± 0.28 , 0.91 ± 0.05 and 0.88 ± 0.64 ng/ml respectively; on day 8 the peak plasma level of clonidine was 0.82 ± 0.28 ng/ml at 6 h. The trough plasma levels of clonidine on days 2, 3, 4 and 5 were 0.56 ± 0.32 , 0.71 ± 0.22 , 0.72 ± 0.18 and 0.47 ± 0.24 ng/ml respectively, indicating no accumulation of clonidine during the study.

The plasma elimination half-lives of clonidine calculated following the last dose of alinidine (day 8) were 14.0 ± 3.7 h (40 mg daily) and 12.6 ± 3.6 h (40 mg twice daily).

The peak and trough plasma levels of clonidine after alinidine 40 mg twice daily did not fluctuate to the same extent as after alinidine 40 mg daily. Alinidine and clonidine had virtually disappeared from the plasma 48 h after the last dose of alinidine.

Twenty-four hour urine samples were collected on days 5, 6, 7 and 8 following administration of 40 mg alinidine either daily or twice daily. The total amount of alinidine and clonidine eliminated for each 24 h period is shown in Table 3. No significant differences ($P < 0.05$) in elimination occurred between days 5, 6, 7 and 8, following 40 mg daily and between days 5, 6, 7 and 8 following 40 mg twice daily.

The amount of clonidine eliminated on days 5, 6, 7 and 8 during administration of alinidine 40 mg daily and twice daily is shown in Table 3. No significant changes occurred in the elimination of clonidine on days 5, 6, 7 and 8 following alinidine 40 mg daily; following alinidine 40 mg twice daily the clonidine elimination on day 5 was slightly higher than on day 6, 7 and 8.

The validity of the three compartment model was tested by simulating the plasma levels following multiple dosing of 40 mg given orally every 12 or 24 h, these curves were calculated on the basis of the data generated from the acute studies. Figure 3 demonstrates the agreement between the mean theoretically predicted curves and the experimentally

Table 3 Mean ($\pm$ s.d.) urine elimination of alinidine and clonidine for days 5, 6, 7 and 8 following chronic administration of alinidine 40 mg daily ($n = 5$) and 40 mg twice daily ($n = 4$) to healthy subjects.

Time	Alinidine 40 mg daily		Alinidine 40 mg twice daily	
	Alinidine (μ g)	Clonidine (μ g)	Alinidine (μ g)	Clonidine (μ g)
Day 5	$22,954 \pm 5335.8$	30.9 ± 5.8	$58,629.5 \pm 14,427.0$	72.7 ± 20.6
Day 6	$20,962 \pm 3893.8$	30.7 ± 8.4	$50,435.5 \pm 13,306.0$	58.3 ± 18.3
Day 7	$21,829 \pm 5328.2$	31.2 ± 12.7	$49,847.0 \pm 12,886.3$	47.4 ± 15.8
Day 8	$26,056 \pm 7967.9$	34.6 ± 10.3	$45,916.2 \pm 11,775.4$	49.9 ± 13.4

Figure 3 Computer simulated plasma concentration curves of alinidine assuming chronic oral administration of 40 mg alinidine given once daily (a) or twice daily (b) based on the acute study. The experimentally obtained plasma concentrations determined in the five healthy subjects (A = $\blacktriangle$, B = $\blacksquare$, C = $\blacklozenge$, D = $\circ$, E = $*$) are shown.

determined individual plasma concentrations of alinidine; following alinidine 40 mg once daily the peak and trough values of the theoretical curves were 225 and 5 ng/ml compared with the experimental values of 233 and 9 ng/ml respectively; following alinidine 40 mg twice daily the peak and trough values of the theoretical curves were 320 and 35 ng/ml compared with experimental values of 356 and 80 ng/ml respectively.

Discussion

These observations show that alinidine is rapidly absorbed after oral administration reaching a peak

plasma concentration at 1.8 ± 0.7 h. Comparison of the AUC after oral and intravenous administration showed that alinidine had a bioavailability after oral administration of around 100%. The plasma elimination half-life after intravenous administration was 4.2 h. The chronic dosing study was designed to see if accumulation of alinidine or clonidine occurred. There was no evidence of accumulation of alinidine during the 8 days. In this study the peak plasma concentration with both dosing regimes was higher on day 2 than on day 1 but remained steady from day 2 to day 8.

The most interesting finding in the present study was that small amounts of clonidine were detected and measured in plasma and urine samples after both

routes of administration of alinidine. The peak plasma concentrations of clonidine were higher after intravenous (0.5 ± 0.22 ng/ml at 4.5 ± 2.5 h) than after oral (0.26 ± 0.06 ng/ml at 8.4 ± 2.2 h) administration of alinidine 40 mg. The levels of clonidine fell slowly from these peaks. Higher plasma concentrations of clonidine were obtained in the chronic dosing study with steady state being reached by the second day with both dosing schedules. The levels were higher with the schedule of 40 mg twice daily reaching mean concentrations of 0.8–1.0 ng/ml, which is in the range occurring after oral administration of the therapeutic dose (300 μ g) of clonidine (Davies *et al.*, 1977).

It is most unlikely that the pharmacodynamic effect of alinidine in man results from clonidine which has been formed. Alinidine unlike clonidine slowed the rate of spontaneously beating isolated atria and reduced heart rate in anaesthetised animals within 5 min of intravenous administration when it would be most unlikely that any significant amounts of clonidine had been formed (Kobinger *et al.*, 1979a,b). Previous studies from this Department have shown that the maximum reduction of an exercise tachycardia occurred 1 h after the oral administration of alinidine 40 mg and declined during the succeeding 5 h. In the present study the plasma concentration of clonidine after oral administration of 40 mg alinidine progressively increased during the first 3 h and although the maximum value was not reached until 8 h there was little difference between the concentrations from 3 to 12 h. In contrast the maximum plasma concentration of alinidine occurred at 1.8 h and then declined. Thus the effects of alinidine on an exercise tachycardia more closely follow the plasma concentration profile of alinidine than of clonidine.

Furthermore the haemodynamic effects of alinidine are different from those of clonidine. The most marked effect of alinidine is the reduction of an

exercise tachycardia with smaller reductions in heart rate in the supine and standing positions and small reductions in systolic and diastolic pressure after 80 mg alinidine. Clonidine (0.1 mg) produced small but non significant reductions in exercise heart rate with no change in standing heart rate and with reductions (significant in standing position) in arterial pressure (Harron *et al.*, 1981). A larger dose of clonidine (0.3 mg) given orally to normotensive subjects in the supine position produced no change in heart rate but a reduction of 20 mmHg in systolic pressure and of about 15 mmHg in diastolic pressure (Davies *et al.*, 1977). Clearly the haemodynamic effects of alinidine and clonidine are different and thus clonidine formed metabolically from alinidine does not account for the pharmacological effects of alinidine in man.

In a previous study (Harron *et al.*, 1981) the subjects complained of drowsiness occurring about 10 h after the oral administration of 80 mg alinidine and to a lesser extent after 40 mg. Some subjects complained of a dry mouth. Similar adverse effects occur after clonidine. It may be that as these effects were more closely related to the peak plasma level of clonidine than alinidine that they were produced by clonidine. In the chronic dosing study tiredness occurred during the first few days of treatment but then disappeared even though the plasma concentrations of clonidine were maintained.

Further studies are required to determine the variations which occur between subjects and in the same subjects at different times in the formation of clonidine from alinidine and the contribution which clonidine may make to the therapeutic effect of alinidine in angina and hypertension.

This work was supported by a grant from Boehringer Ingelheim Ltd, Bracknell, England. We are grateful to Dr K. Jady for his help.

References

- ARNDTS, D. & FORSTER, H.J. (1982). New aspects in the metabolism of alinidine in man. *Eur. J. Metab. Pharmacokin.* (in press).
- ARNDTS, D. & STAHL, H. (1982). Development and quality control of a highly sensitive radioimmunoassay for alinidine. *J. pharmac. Methods* (in press).
- ARNDTS, D., STAHL, H. & FORSTER, H.J. (1981a). Development of a RIA for clonidine and its comparison with alternative reference methods. *J. pharmac. Methods*, **6**, 109–120.
- ARNDTS, D., WARNKROSS, H., ROMINGER, K.L. & JUSTUS, H. (1981b). Linearity proof of the pharmacokinetics of alinidine in man. *Eur. J. clin. Pharmac.*, **21**, 201–207.
- DAVIES, D.S., WING, L.M.H., REID, J.L., NEILL, E., TIPPETT, 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., RIDDELL, J.G. & SHANKS, R.G. (1981). Alinidine reduces heart rate without blockade of β -adrenoceptors. *Lancet*, **i**, 351–353.
- KOBINGER, W., LILLIE, C. & PICHLER, L. (1979a). N-allyl-derivative of clonidine, a substance with specific bradycardic action at a cardiac site. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **306**, 255–262.
- KOBINGER, W., LILLIE, C. & PICHLER, L. (1979b). Cardiovascular actions of n-allyl clonidine (ST567), a substance with specific bradycardic action. *Eur. J. Pharmac.*, **58**, 141–150.
- WOLF, M., HEINZEL, G. & KOSS, F.W. (1977). Pharmacokinetic II. Teil: Verallgemeinerte theoretische Darstellung der vollständigen Interpretation linearer Kompartimentmodelle beliebiger Struktur. *Arzneim. Forsch. (Drug Res.)*, **27**, 900–1004.

(Received October 30, 1981)